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ELECTROENCEPHALOGRAPHIC CHANGES IN ANIMALS UNDER THE INFLUENCE OF HYPNOSIS[1]

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Animal hypnosis is a motionless state of generalized rigidity associated with a reduction in responsivity to environmental stimuli. It has been described as occurring from coelenterates to mammals. Although Verworn first used the term "animal hypnosis", it also has been known as "mesmerism", "fascination", "entrancement", "death feint", "cataplexy", "catalepsy", "conscious simulation of death", "immobilization reflex", "conditioned akinesia", "hypertonicity", "tonic immobility", "inhibitory state", "inhibition" and "playing possum" (5, 9). Furthermore, animal hypnosis has been compared to catalepsy and catatonia in human beings. Despite a relatively voluminous literature on the subject dating to Abbe Kircher's investigations of the hen in 1646, Pavlov's (14) statement is still highly pertinent: "Little has been done towards the elucidation of the class of negative or inhibitory reflexes (instincts) which are often evoked by any strong stimulus or even by weak stimuli if unusual. Animal hypnosis so-called, belongs to this category."

Although animal hypnosis presumably is a state mediated by neuronal mechanisms, scant neurophysiologic research in this area has been undertaken. The general references concerned with animal hypnosis are chiefly in German and French.

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The related literature reveals essential harmony concerning a definition of animal hypnosis, the technic of inducing the trance, and the duration of the effects. The chief factor in the induction of the trance is restraint of motion. Other factors are bodily posture, fixation of the eye, repetitive tactile or visual stimulation and sudden shock or concussion (4, 5). Although states analogous to animal hypnosis have been produced in some species by surgery or facilitated by drugs, these are not true prerequisites to the condition.

Some aspects of animal hypnosis that have been studied in different species and with varying and at times controversial results are heart rate, respiration and analgesia (2, 6, 11, 18). The results are too uncertain to be accepted as constant concomitants to the condition of any one animal.

Studies arising from work in extirpation and ablation can best be summarized as indicating that a deep midline structure in the brain or phylogenetically primitive area is responsible for catalepsy. For example, Verworn and Danilewski (21) noted no changes in susceptibility to hypnosis in frogs from which both hemispheres had been removed. Gilman and Marcuse (5) reported no changes in susceptibility to hypnosis in animals from which the vestibular centers had been extirpated. Mangold (10) wrote that hypnosis could be brought about in birds and mammals without a cerebrum. Barris (1) produced catalepsy in cats by the infliction of bilateral cortical lesions. Speigel and Goldglom (19) claimed that presence of the red nucleus is essential for catalepsy, and Hoagland (8) could produce catalepsy in anolis by thrusting a needle into the fourth ventricle.

One of the many theories which attempt to

explain this phenomenon is Pavlov's (12, 15). He believed that animal hypnosis is essentially a form of sleep. His views were shared by Heubel (7), Wundt (23), Trömner (20) and Sidis (18).

The Present Study

In an attempt to clarify this problem, electroencephalograms of a bullfrog and three guinea pigs were made while they were in the cataleptic state. It was felt that if catalepsy or animal hypnosis was related to sleep, the electroencephalogram would show some changes since it is a sensitive indicator of drowsiness and sleep states. In a review of the literature no references were discovered that dealt with this method of study.

Method. One bullfrog and three female guinea pigs were selected on the basis of ability to become cataleptic in the hypnotic trance. All the animals were fully grown and mature. Hypnosis was defined as "a rigid, immobile state with a generalized reduction in responsivity to the environment." For the purposes of this study, a state of immobility was considered satisfactory if it persisted 20 seconds or longer.

The method of inducing the trance followed technics used by previous investigators. The frog and guinea pigs were hypnotized by being firmly grasped and suddenly turned over on their backs. If necessary, the abdomen was stroked gently.

All the experiments were conducted in a fairly quiet, uniformly lighted, air-conditioned room at 70°F. While the animals were hypnotized by the observer, an assistant wrote on the electroencephalographic record observations on the behavioral state of the animals.

Satisfactory electroencephalographic records cannot be made on small animals without implanted leads. The animals were therefore prepared as follows: While the frog was under the influence of refrigeration anesthesia, permanently implanted silver electrodes were placed extradurally and fixed in position with acrylite. The areas from which tracings were made were the olfactory bulb, right and left cerebral hemispheres and optic lobes. A reference electrode was inserted under the skin over the rostral cervical vertebrae. Both monopolar and bipolar tracings were made simultaneously.

In the guinea pigs stainless-steel electrodes were placed extradurally in the anterior, middle and posterior regions of each hemisphere and fixed with acrylite. Bipolar recordings were made in these instances. This technic is described elsewhere (17).

Recording. The electrodes from the bullfrog were individually soldered to wires 3 feet long, and similar connecting wires were used with the other animals, except that they were directly inserted via a plug into the acrylite-fixed skull socket. For most of the studies the electrode wires were connected with a type A Offner crystograph amplifier and inkwriter. Many of the studies on guinea pigs were done with 6 channels of an 8-channel Grass type III electroencephalographic apparatus. At this time an Ediswan automatic-frequency analyzer was used (3). The calibration of the Offner and Grass machines was so adjusted that an excursion of 0.5 cm. in the pens equaled 100 microvolts. The frequency analyzer was calibrated so that an input of 100 microvolts signal at all tested frequencies between 1.5 and 30 cycles per second and of 1 cm. peak-to-peak amplitude yielded a constant excursion of 6.3 cm. in the analyzer pen.

Bullfrog

The bullfrog was hypnotized and rendered cataleptic 38 times in 56 trials on 6 different days. It remained completely immobile in a rigid state with the eyes wide open for as long as 5 minutes. During this time it was apparently unresponsive to stimuli such as the ringing of a telephone, people entering the room and talking, light flashing in the eyes, and gentle touching of the body. It could be aroused by any sudden and unusual stimulus, such as a loud clap or painful pinching. At no time did it close its eyes. In the control state and at other times the frog always withdrew at the approach of the observer. Its eyes were always open. It never seemed to sleep, in the sense that higher animals do, meaning eyes closed and relative unresponsiveness to the environment.

Results. During the control state, while the frog was sitting on the table or in a jar, the electroencephalogram showed high-voltage (100 to 200 microvolts), 7-to-9-cycle-per-second activity maximal from the cerebral hemispheres. This activity persisted for periods as long as 10 minutes. This activity was also present when the frog was on his back and not cataleptic. Unless the frog was restrained, this state of non-catalepsy while on his back never lasted longer than a few seconds.

Always within 10 seconds and usually simultaneously with the onset of the cataleptic state, the electroencephalogram showed changes. These appeared as 50-to-100-microvolt, 5-to-7-cycle-per-second waves maximal from the cerebral hemispheres and optic lobes and associated with some flattening of the background and disappearance of the 7-to-9-cycle-per-second normal background rhythm. With progressively longer and deeper stages of catalepsy these changes became more prominent and generalized over the brain. They remained fairly constant in amplitude

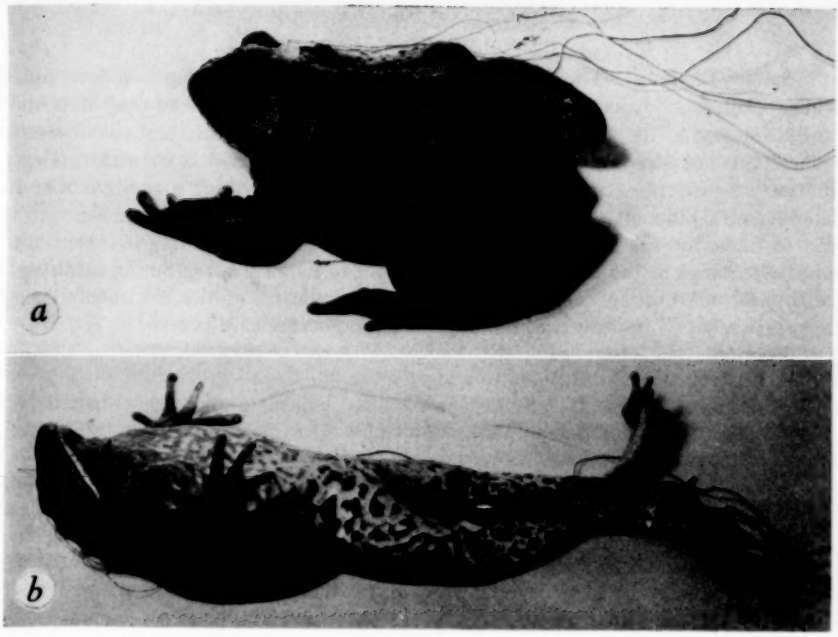

FIG. 1. *a*. Bullfrog in the alert state; *b*. bullfrog in the cataleptic state.

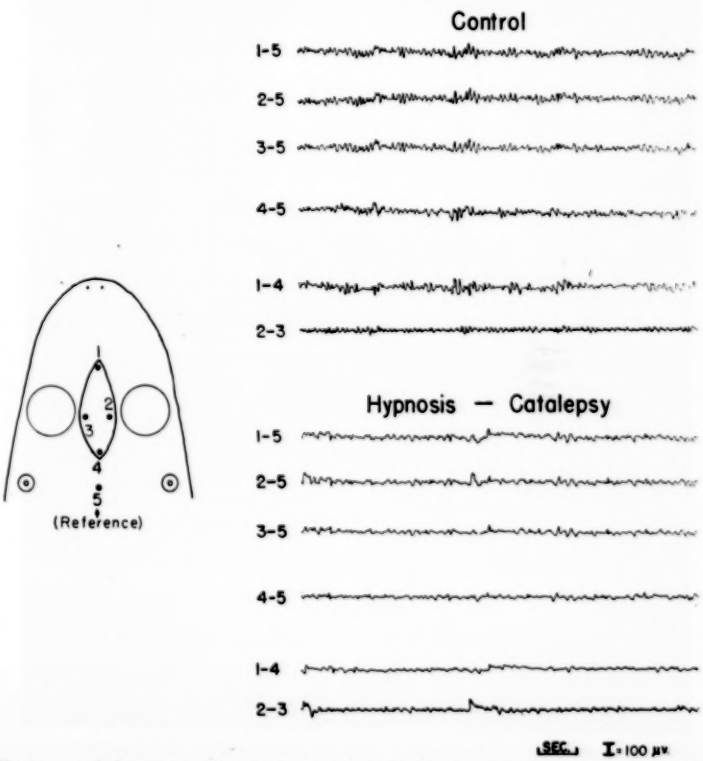

FIG. 2. Electroencephalogram produced from a frog during consecutive alert and cataleptic states.

during the time of hypnosis. The immediately successive electroencephalographic changes from the cataleptic to the control state were more consistent and striking than from any one control or cataleptic tracing compared with another of a different sequence or day. The end of catalepsy was always marked by an immediate change in the electroencephalogram which resembled the control recording.

With practice, visual inspection of the electroencephalogram was often sufficient for distinction between the control state and catalepsy, without identifying legends. The constant finding was the difference in the electroencephalogram as between catalepsy and non-catalepsy, rather than constant identical electroencephalographic changes for each episode of catalepsy.

With all the trials there was no apparent change in susceptibility to catalepsy, judged by either its intrinsic depth or total duration. Seldom in the upright control state did the frog exhibit the concomitant electroencephalographic changes associated with catalepsy. It did not show anything suggestive of or analogous to the sleep of higher animals.

Figure 1*a* shows the frog in a control state; figure 1*b* shows the frog during catalepsy; and figure 2 illustrates the electroencephalogram at these consecutive times.

Guinea Pigs

One guinea pig, a short-haired albino, readily went into a cataleptic trance 15 times in 25 trials on three different occasions. During catalepsy it remained motionless on its back, with its head and legs rigidly hyperextended, and eyes staring for periods lasting as long as 3.5 minutes. There was no apparent change in breathing. This guinea pig and two others

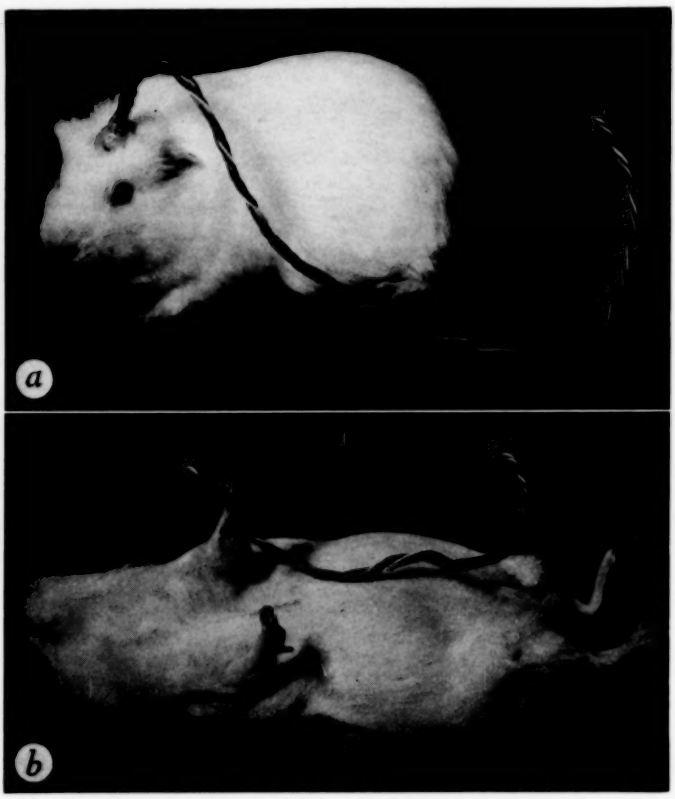

Fig. 3. *a*. Guinea pig in the alert state; *b*. guinea pig in the cataleptic state.

which were studied did not close the eyes or give evidence of being asleep as the higher mammals sleep.

Results. When the guinea pig was in the upright, alert state, the electroencephalogram showed 7-to-9-cycle-per-second, 75-to-100-microvolt activity, mixed with infrequent high-voltage, 1-to-3-cycle-per-second activity, maximal from the midhemispheric regions. This activity persisted for periods as long as 10 minutes. When the guinea pigs were on their backs and not cataleptic, the electroencephalogram showed no appreciable change in comparison with that made in the upright control.

During catalepsy, and usually simultaneous with the onset of the rigid posture and always within 10 seconds, the electroencephalogram showed a tendency toward background flattening and toward the occurrence of 100-to-200-microvolt, 1-to-3-cycle-per-second waves most prominent from the midhemispheric regions. Mixed with this frequency there also was 75-to-100-microvolt, 6-to-11-cycle-per-second activity. With increased duration and depth of catalepsy the record was still more distinguished from that of the control. Changes in areas other than the midhemispheric regions were less well circumscribed and apparent. However, the cataleptic state could almost always be distinguished from the control state by inspection of the electroencephalogram. With cessation of catalepsy the record always changed immediately. Repeated trials did not seem to influence either the susceptibility of the animal to the trance or the duration of the trance. At no time during the control periods between catalepsy or at other

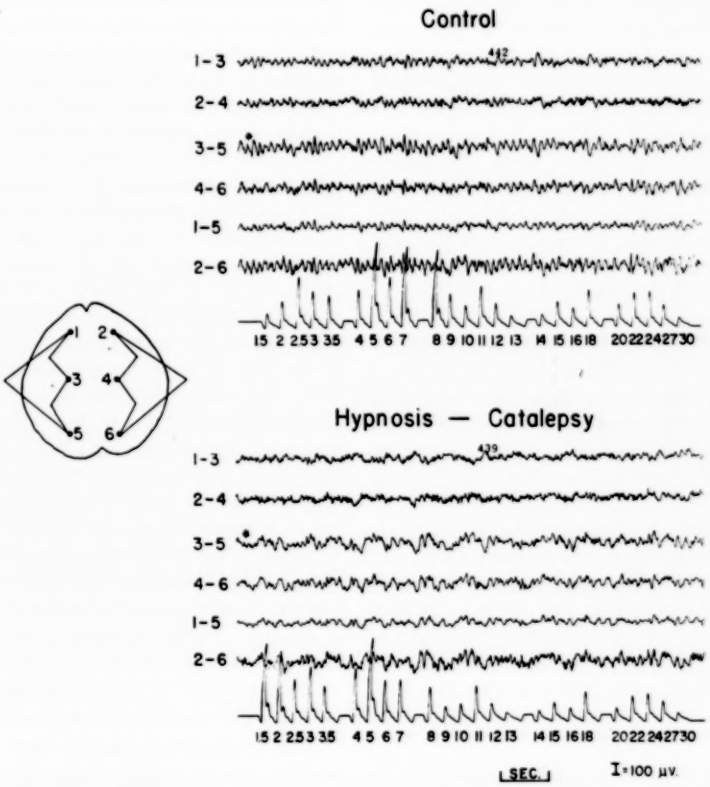

FIG. 4. Electroencephalogram produced from a guinea pig during consecutive alert and cataleptic states.

* Automatic frequency analysis of the left midhemispheric-posterior hemispheric area.

times were the relatively abrupt electroencephalographic changes evident.

Automatic Frequency Analysis

Because of difficulty in clearly defining the electroencephalographic changes during catalepsy, automatic frequency analysis was employed. The albino guinea pig was hypnotized 14 times in 23 attempts at analysis of the left midhemispheric-posterior hemispheric region. Two pigmented, short-haired guinea pigs were rendered cataleptic on three of 23 and six of 28 attempts, respectively. The pigmented guinea pigs struggled and wriggled incessantly. Once the black guinea pig bit the observer. In further contrast to the albino guinea pig, the pigmented animals yielded a control electroencephalogram that was of approximately a third the voltage and had much 20-to-25-cycle-per-second activity, maximal in the anterior regions of the head. Analysis of the right frontal-midhemispheric area was carried out in both of the pigmented guinea pigs because this area afforded the best technical record.

Results. In the control state, frequency analysis revealed low-amplitude deflections in the 1 to 3 frequency and prominent, high-amplitude deflections in the 4 to 7 frequencies. This was also noted to persist when the guinea pigs were on their backs and not cataleptic.

In all instances of catalepsy there was a shift to the delta band and diminution in the height of the pen deflection in the 4 to 7 and 8 to 13 band frequencies. Automatic frequency analysis indicated that the catalepsy occurred either completely or not at all, and that the depth of the trance was not always at the same level.

The upright, alert state of the guinea pig is shown in figure 3*a* and the cataleptic trance in figure 3*b*. The electroencephalogram, with automatic frequency analysis of the left midhemispheric-posterior hemispheric area during these two consecutive states, is illustrated in figure 4.

Comment

Consideration of the results obtained on the various animals in which a hypnotic state could be induced indicates that a change in brain-wave pattern accompanies the induced state. In all instances this consists of a replacement of the background (alpha) rhythms by slower frequencies, these changes being diffuse in distribution (it will be recalled that the number of recording points was limited). This certainly suggests a neurophysiologic correlate of the cataleptic state.

The question now arises as to whether the changes in brain waves can be considered to be in any sense specific or whether they might be related to some change in the animal's state of attention. The theory that catalepsy represents a "death feint" presumably would indicate that the animal would be in an excessively alert and anxious condition. Observations on both human beings and animals indicate that the state of alertness is associated with a diffuse, fast pattern quite different from those exhibited by our animals under hypnosis. This might be taken as evidence against the theory that the cataleptic state represents a "death feint" in which anxiety and alertness might be expected to be prominent features.

Other authors have thought that catalepsy is more closely related to the sleep states, and this theory would certainly receive some support from our findings. The disappearance of background rhythms, followed by the appearance of slower waves, which was seen in the hypnotized animals is a change which is characteristic of the onset of drowsiness in animals and human beings. While data are not available on the form of drowsiness rhythms in the frog, it would be a reasonable supposition that such rhythms would follow the general pattern produced in other animals. A similar interpretation might be suggested in the case of the guinea pig. Nicholls (13) concluded that guinea pigs never sleep in the sense that higher mammals sleep. On the contrary, when fatigued, they eat and move about, rather than sleep. It would seem, therefore, that we are not faced with the necessity of postulating a specific rhythm associated with hypnosis, but can regard our findings as reflecting a changed state of consciousness probably analogous to the onset of drowsiness.

The fundamental question now arises as to whether the drowsiness state is instrumental in producing catalepsy or whether it is merely a by-product of the cataleptic state. Introspective data from the human being and some

other studies in hypnosis by means of the electroencephalogram (16) would raise the question as to whether the cataleptic state could be related to the well-known sleep paralysis occurring in certain stages of drowsiness in the human being. This relationship has been suggested by Wilson (22). The question is difficult to answer on the basis of our findings.

The fact that the changes in brain waves almost invariably followed a short lag after the induction of hypnosis would seem to indicate that some other unknown phenomenon already has taken place, with drowsiness as a consequence.

Summary and Conclusions

1. By means of animal hypnosis, the cataleptic state was produced in one frog and three guinea pigs on many occasions. During catalepsy the electroencephalogram exhibited a slowing in frequency and a tendency for the background rhythms to disappear. This change was confirmed in the three guinea pigs when automatic frequency analysis was carried out.

2. It is thought that catalepsy in the frog and guinea pig is a state closely related to drowsiness.

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AN INQUIRY INTO THE MECHANISM OF ACTION OF ELECTRIC SHOCK TREATMENTS

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Perhaps the earliest shock therapist was Scribonio Largo, in 45 A. D., who treated headaches by placing torpedo-fish on his patients' heads (16). The first real electric shock treatment was given by Dr. J. B. LeRoy in 1755 (44); and by the last half of the nineteenth century, electrotherapy had become a recognized form of treatment. However, modern electric shock treatment was not developed until Sakel and Meduna published their papers, in 1933 and 1935, on insulin coma and metrazol convulsions (66d). The therapeutic value of these new methods soon became apparent, but they were cumbersome and difficult to control. When Ugo Cerletti introduced electrically induced convulsions in 1938, the new method was rapidly taken up throughout the world.

Since then the technique has been much modified. Muscle relaxants, sedatives and anesthesia have reduced fractures, fear and apnea (103). Much attention has been given to the type of electricity used and its method of administration. The hope is that thereby undesirable side effects can be eliminated and more specific results achieved. Thus brief stimulus techniques (73), electronarcosis, unidirectional currents (30), unilateral electrodes, post-convulsive stimulation, and non-convulsive stimulation have all been tried (3b, 3e). Variations in current include alternating and direct, glissando or slowly increasing the current, square waves, sine waves, exponentially rising and falling currents (3d, 82). The electrodes have been placed inside and outside the skull and all over the body.

In summary, electric shock treatment with all its protean modifications has become, in less than twenty years, the most widely-used shock therapy in psychiatry. One question is—does it do any good? It is very difficult to test just how effective any psychiatric treatment really is. For example, many mental diseases clear up spontaneously. On the other hand, no one knows when EST has failed because some patients recover only after many convulsions.

One reliable end point is death! EST significantly reduces the number of suicides in mental patients (92, 113). Shock therapy may be of value in hysteria, obsessive-compulsive states, etc. (66d). The procedure was introduced to treat schizophrenia, and some still feel that its greatest effectiveness is in this disease (25). Certainly, EST is of use in schizophrenia, either alone or in combination with other treatment (21a, 66d).

However, the main indication for EST today is in the manic-depressive disorders. Here, it cuts the average hospital stay by more than half (11). In New York State, for example, 70 per cent of treated patients spent less than two months in the hospital, while only 18 per cent of pretreatment controls were in the hospital under two months (84). In all, more than ninety per cent of manic-depressive patients recover or improve with electric shock treatment (9, 103).

Whether or not these patients stay cured is debatable. On a one year basis, treated patients have less relapses (84). But some physicians maintain that the effect of EST is only temporary (9, 90). Bond's series, for example, shows that at the end of five years the untreated and treated groups have about the same percentage in remission—65% (11). On the other hand, Fetterman, by repeat courses of EST, managed to keep about 80% of patients in satisfactory remission after six years (33).

For the purposes of this paper, it can be said that EST shortens the course of manic-depressive psychotic episodes. How is this achieved?

In 1948 Gordon was able to collect 50 theories on the mechanism of action of EST from the literature (40). There are probably many more extant today. These theories divide roughly in half between the somatic and the psychodynamic (40). The latter largely arise from psychoanalytic concepts. A theory of this type, current in Boston, is that fear of the convulsion produces the therapeutic effect (12). Yet, most successfully treated patients are unaware of their convulsions. Furthermore, when psychiatric patients are given acetyl-

choline intravenously, horrible twitchings and choking sensations result; fear runs rampant. But the patients fail to improve (45). In general, it can be said that these psychodynamic theories by their very subjective nature admit of no proof or disproof (79b).

Therefore, I will deal only with the somatic or organic theories of the mechanism of action of electric shock treatment. These can be divided into six categories: mechanical or structural, endocrine, nutritional, autonomic, changes in permeability, and miscellaneous.

The structural concepts state that EST affects the deep elements of the brain (66b, 66c), where it kills diseased cells (10, 38c, 58, 68). The convulsion may "blow asunder the pathological sequences and restore the diseased organism to normal functioning." (79a). A favorite site for this action is the diencephalon where "subtle structural alterations" are supposed to occur (58, 90, 92). In other words, the diencephalon is "massaged or exploded" (12). By analogy with prefrontal lobotomy, some feel that the frontothalamic tracts are damaged. The advantage of these structural concepts is that they explain the relatively lasting effect of EST.

The pituitary-adrenal axis is stimulated during the course of the convulsive therapy (5m, 6a, 54). The endocrine theories postulate that this system may be abnormal somewhere along the line in psychiatric disease and may be renovated by EST (5b, 5d, 54). The occurrence of psychoses with the administration of adrenal steroids suggests that shock treatment acts by suppressing the adrenal (5d). Another hormone, progesterone, has been said to cure post-partum psychosis; perhaps it too acts by depressing a hyperactive adrenal (13). It may be that the diminished ovarian function, which occurs with EST, is therapeutic (5g). Still another hormone, testosterone, is apparently beneficial in mental disease. By analogy, EST may likewise produce an anabolic, reparative effect (5a). Finally, pineal gland extracts are said to cause improvement in psychoses (5l, 5j). All this hormonal evidence is suggestive, but endocrine changes in EST do not correlate well with clinical recovery, and they do not explain the specific action of convulsions.

During the course of a convulsion, relative anoxia probably occurs locally in the brain (38b, 52c). Many investigators feel that this oxygen lack produces the therapeutic effect, perhaps by a specific action on higher cortical centers (10, 52b) or by stimulation of autonomic ganglia (38a). It may be that the anoxia lowers cerebral metabolism during the fit and leads to post-ictal hyperactivity (35, 52a). Yet, such anoxic states as cardiac arrest, asphyxia and nitrogen administration have no influence on mental disease (45). So it seems probable that anoxia is of minor therapeutic importance (14b, 41b, 59b, 67b). Indeed, oxygen administration prior to EST not only prolongs the fit, but may improve its effectiveness (59b). Holmberg and Weil-Malherbe emphasize the importance of distinguishing between the primary effects of EST—namely neuronal discharge—and the secondary effects such as the muscular contractions, oxygen deficiency, fractures or memory loss (59a, 59b, 107). It seems to be the neuronal discharge that is important.

Perhaps the most popular group of EST theories has to do with the autonomic nervous system. This is natural in view of the wild vegetative reactions which occur during a convulsion (3c, 57, 107). Also, Funkenstein's prognostic tests seem to tie the autonomic nervous system in with mental disease (3g, 37a, 37b). These ideas, then, assume that the parasympathetic and/or sympathetic nervous systems are stimulated by EST—probably via the hypothalamus (38a, 38c, 48) or the cingulate gyrus (65). Such stimulation may correct an autonomic imbalance (109). As Pfister has stated, shock treatment may restore "to fertility the fallow field of vegetative function." (10). However, the degree of apparent autonomic stimulation does not correlate well with the degree of clinical recovery (3b, 3e, 53).

There is a growing awareness of the importance of membrane phenomena in biology and especially in impulse transmission (28). The fifth group of EST theories postulates that change in membrane permeability lies behind the therapeutic effect (2a, 2b, 3a, 95b). There is considerable evidence for this idea which will be presented below.

There remains a heterogeneous group of theories of the mechanism of action of shock treatment. Sackler *et al.* feel that histamine is important (91). Danziger has proved mathe-

matically if not chemically that EST destroys a psychotic toxin (21b). Cerletti has injected suspensions of shocked pig brains in phenolic water into 36 patients; this produces "remarkable changes" which he attributes to curative substances called acroagonines (16). There are theories of toxin wash-out, cortical depression, multiple etiology (68), inhibitory influences (109), organ activation (67b), and so forth.

All of these theories tend to break down when applied to the clinical situation for the following reason: they fail to explain why a convulsion is necessary to cure depression. There are two main lines of evidence which clearly demonstrate that a convulsion is the *sine qua non* in successful EST.

First, whether patients are given electricity, metrazol, aminophylline, camphor, picrotoxin, caffeine, or perhaps even insulin (58), the clinical results are the same as long as a convulsion occurs (10, 66d). The type of current and method of application seem to be of secondary importance (17, 81a). It must be remembered that EST was developed as a simple way to produce a convulsion, not as a new approach to psychiatric treatment. Furthermore, convulsions, epileptic or iatrogenic, seem to be basically the same (66a, 70, 85) although there are some findings to the contrary (8b, 50, 86b, 105, 112). In other words, very different types of convulsant agents produce roughly the same type of convulsion and are equally effective therapeutically.

There is a second line of evidence. In the experience of most psychiatrists, any form of electric stimulation which fails to produce a convulsion will not cure depressions (3b, 9). Indeed so-called subconvulsive stimulation may aggravate the psychosis (3e, 113). On the other hand, when, and only when, convulsions do occur, patients get better (3c, 60, 80, 92, 104, 108).

It is interesting that Meduna developed convulsive therapy because he believed that there was a "biological antagonism" between epilepsy and schizophrenia (79a). This concept has been proved and disproved many times since 1935 (3e, 15, 55, 56, 67a, 68). However, the coincidence of manic-depressive psychosis with epilepsy has apparently never been investigated. It may well be, as Flescher has said, that "the mechanism of EST cannot be understood unless the function of the spontaneous epileptic attack is first understood." (35).

It seems fair to say then that the convulsion is the essential factor in EST (even if it is only an indicator of some more fundamental underlying process) (30).

The question of the mechanism of action of EST now resolves itself into two phases: one, how does EST produce a convulsion; and two, how does a convulsion cure depressions?

The first problem then is to determine the events which follow the passage of current through the head and lead to the onset of a convulsion. In the usual patient, an electric shock first produces a brief tonic spasm followed by a relaxed so-called latent period for several seconds, then the tonic phase of the convulsion occurs, and finally the clonic phase. The whole process takes about 45 seconds (34).

It seems desirable, first, to determine what happens to the electric current. The most widely held theory is that the current travels directly between the two electrodes (3e). Postmortem studies and vascular changes tend to support this idea (3a, 3e). However, Hayes and others feel that most of the current circles the head in the skin. What little electricity manages to penetrate the high resistance of the skull is refracted so that the whole brain is diffusely stimulated (17, 47, 94). Other theories are that the current concentrates along blood vessels (2a) and ventricles (46), or that the current follows nerve tracts such as the corpus callosum (30).

A problem related to the current path is whether or not it is necessary to stimulate specific structures to produce a convulsion. The following areas have been said to be epileptogenic: the superior frontal gyrus (20), the motor cortex (30), limbic cortex (30), cerebral cortex as a whole (clonic) (3d), temporal lobe (73), subcortical gray matter (tonic) (3d), caudate nucleus (30), mesencephalon (58), diencephalon (3e), midline structures (90), cerebellum (86c), area postrema (63), and spinal cord (42). However, many feel that convulsions are not caused by a localized convulsive center (42, 66c). Certainly many different kinds of stimuli, in many different parts of the central nervous system will produce convulsions. Also convulsive potentials ap-

pear simultaneously over the entire cortex prior to a fit (105). However, when decerebrate cats are given absinthe, intravenously, only a tonic fit results (10). This suggests localization in the sense that the cerebral cortex is necessary for the clonic phase (98). By and large though, convulsions probably arise from a diffuse process.

Another approach to the question of how EST produces a fit is provided by the study of the electrical requirements. The property of responding to an electric stimulus by increased metabolism *in vitro* (75b, 75c) or by convulsions *in vivo* is unique with nervous tissue (71). The amount of electric energy required to produce a convulsion depends upon many factors: the cerebral hydrogen ion concentration and hydration, the patient's age, sex and temperature, the number of previous treatments, etc. (17, 66a, 66d, 77b, 80, 95d, 100, 101b). Once a fit has started, however, it runs its course despite all electric efforts to the contrary (3e). (Continued stimulation may depress the clonic phase of a convulsion (3e).) In general, then, convulsions tend to follow an all or none pattern, with a certain minimal current requirement to set them off (50, 101a).

There are several processes which go on in brain when an electric current passes through it. For example, an increase in cell membrane permeability seems to occur, allowing potassium ions to leave the neuron prior to a convulsion (31, 77a). Several authors interpret this to mean that a change in cell membrane permeability is the cause of a convulsion (18, 77a, 95a). McQuarrie, in particular, feels that all convulsants actually influence the surface functions of brain cell membranes (77a).

Some investigators postulate that acetylcholine has a role in the central nervous system as a transport molecule (29e). Richter and others have shown that the cerebral actylcholine content falls with electric stimulation (29c). Oddly enough, the acetylcholine concentration then returns to normal before the the convulsion occurs (89b). Anticonvulsants, on the other hand, increase cerebral acetylcholine content (102d). Elliott has found that epileptic human cortex fails to produce the storage form of acetylcholine normally. This could result in a tendency for the free acetylcholine, a convulsive agent (36), to be liberated and produce convulsions (87, 102c). Finally, McIlwain finds that atropine prevents the normal brain tissue response to electricity (75e). All of which has suggested to numerous investigators that liberation of acetylcholine plays a part in the electrically-induced convulsion (76).

Another change following stimulation but preceding the onset of a fit is the liberation of ammonia (89a) which has several convulsant-like effects (75f). Richter feels that acetylcholine and ammonia together produce a convulsion (89a). Elliott points out that the synthesis of glutamine from glutamic acid and ammonia may be necessary for the production of bound acetylcholine (102d). But phosphocreatine, an energy-rich compound, is diminished in the brain following stimulation (24). It may be that electric stimulation reduces the availability of energy-rich compounds for synthetic activity.

The roles of carbon dioxide (80, 86c), oxygen (10), and hydrogen ion concentration in initiating and influencing the course of a convulsion are uncertain (22b, 27a, 41b, 62). Oxygen administration may prolong a convulsion (59b), or it may abort it (86a). Carbon dioxide tends to prevent convulsions (86c). Apparently carbon dioxide acts by increasing cerebral blood flow and hence cerebral oxygen tension (8a, 80).

Cerebral blood flow and blood vessel diameter have been said to increase (85), stay the same, or decrease prior to a fit (10, 46, 95b). At any rate, it is certain that stimulation of nerve cells leads to a local fall in oxygen tension and an increase in metabolic products (22a, 23, 97). It seems most likely that these acid metabolites control the cerebral blood flow, and hence that both blood vessel diameter and blood flow would increase. The important point is that all these changes appear to be secondary to increased neuronal function and probably do not themselves cause the convulsion (64, 75a, 75d).

To summarize with regard to the first problem—how does electricity produce a convulsion? Apparently a convulsion occurs whenever a sufficient number of nerve cells are stimulated. It may be helpful to think of the brain as a balance between membrane buildup and breakdown, or rest and function, or energy

production and utilization (75g). Convulsants, in general, seem to act by either speeding up energy utilization or preventing its resynthesis. Electric stimulation shifts the balance in favor of energy utilization or increased function. At a certain level of stimulation, the membrane breaks down completely and a convulsion occurs.

The second and final problem is to study what goes on during and after a convulsion. It is to be hoped that thereby some clue will emerge as to how a convulsion cures depressions and hence how shock treatment works.

One of the most marked effects of a convulsion is an increased output of adrenal corticoids (5i) probably secondary to ACTH production (6b, 54). This is evidenced by diminished eosinophil (5d) and lymphocyte counts, increased uric acid excretion, water retention, diminished carbohydrate tolerance and increased urinary 17-keto steroids (5i). Note, however, that these adrenal cortical effects are most prominent after the first treatment and tend to disappear with each successive convulsion (5f, 6a).

The adrenal medulla is also active during a convulsion—probably secondary to diencephalic stimulation (38a). Weil-Malherbe has found a brief increase in plasma adrenalin and nor-adrenaline following a fit (107). Perhaps related to these adrenal effects are changes in carbohydrate and fat metabolism, blood glutathione level and an acceleration in clotting time (5b, 5c, 5e, 51, 69).

Other hormonal changes include a diminished urinary estrogen excretion and an increased ADH production (5g, 5i). The latter is perhaps a repsonse to post-ictal hemoconcentration which contributes to the high serum sodium, potassium, chloride, protein, and cholinesterase (5i, 7, 18, 88).

As might be expected, blood carbon dioxide rises and oxygen falls during the apnea of a convulsion (3e, 52c, 67a). This anoxemia can be abolished by giving the patient oxygen prior to the convulsion (59b). The cerebral blood flow increases while the blood pressure rises, falls and rises again (14a, 14b, 43).

With regard to the brain itself, a fundamental question has been and still is—do convulsions destroy nerve cells? Some evidence has been gathered from isolated autopsy reports, but these are generally complicated by other diseases and are unreliable (3a, 3e, 4a, 12, 72). The largest series is McLardy's 15 brains which showed no pathological changes (66b). Another source of information is animal experimentation (4b). The errors here are due to agonal changes, similarity with controls, zoonoses, etc. (49). Hartelius, in a very careful study on cats, found perivascular infiltration, glial reaction and nuclear hyperchromatism in the cerebral cortex (46). These changes could be found only one to two days after a convulsion, neither before nor after. Hartelius feels that this time factor means that the changes are associated with a reparative process. He and other investigators think that cerebral anoxia may be the underlying cause rather than the convulsion (49, 74). At any rate, the slow potentials, which may occur after EST and may be related to these changes, are generally temporary and do not correlate with clinical improvement (17). There are, in addition, reports of patients receiving 200 or more treatments without ill effects (66d). In summary, there may be minor, generalized, reversible alterations in the brain structure following a fit.

Hyden describes a more immediate change in nerve cells which occurs following intense stimulation or exhaustion (61). The cell body, nucleus, and nucleolus increase in size, and there is a disintegration of cytoplasmic nucleotides and proteins. This may be associated with the finding of nucleic acids and nucleases in the cerebrospinal fluid of patients after a fit (95e, 96). Acid and alkaline phosphatase activity also change markedly during a convulsion, with an increase in the latter (99). It may be that some non-specific enzyme is converted to alkaline phosphatase (63).

Several investigators have shown that a change in nerve cell permeability occurs in a convulsion (75a, 95c). For example, the concentration of potassium ion increases in jugular blood and cerebrospinal fluid; the sodium ion content decreases (19b). Changes in the opposite direction occur within the nerve cell (19a). This effect lasts about twenty minutes in rats (111). Aird and others have found a change in the so-called blood brain barrier with EST. This results in an increased susceptibility to cocaine. The effect is lasting in cats but can

be reversed by administering trypan red (2a). It would be of interest to know if trypan red would also reverse the clinical response to EST in humans.

The acetylcholine content of brain is affected by many factors such as freezing, death, injury, or anesthetics (29c, 29d, 32, 102a). During a convulsion, acetylcholine appears on the surface of the brain and in the cerebrospinal fluid (102b, 102c). Richter finds a fall in brain acetylcholine during convulsions followed by rapid restoration to normal (89b). Elliott points out that potassium ion is part of the choline acetylase system (29d). Therefore shifts in acetylcholine and potassium concentrations may be related.

Psychologically EST restores inhibited conditioned reflexes in animals (38c) but disorganizes instinctive behavior (5k).

The cerebral metabolic processes that go on in a convulsion depend upon the oxygen supply. Observations on epileptics convulsing on the operating table (10) and on stimulated animals (3a) have demonstrated cerebral vasoconstriction (46). Yet measurements of cerebral blood flow either show no change or an increase (110)—especially in the basal ganglia (85).

Jasper, Dusser de Barrenne, and others have clarified this contradiction (27b, 64, 78). They found that in a convulsion the neuronal activity increases first, followed by an increase in hydrogen ion concentration and lastly by an increase in blood flow (27a). Thus, blood vessels within the brain are probably dilated by the acid products of metabolism.

The increased acidity of the brain during a fit suggests that there is a relative lack of oxygen despite the increased blood flow (52c). Davis *et al.* found a definite fall in cerebral oxygen tension (23, 41b), and Schmidt *et al.* found an increased cerebral oxygen utilization, most marked in the gray matter (68, 93). At the same time, the oxygen saturation falls in the jugular blood (68). It is of interest that the cerebral oxygen tension begins to drop several seconds before the first electrical sign of a convulsion in the cortex; and it reaches its nadir about one-half minute after the last large seizure potential (23).

It is well known that the brain exists on a diet of sugar and oxygen (26, 75h). Jung has calculated that neuronal activity increases about fifty times in a convulsion (46). Therefore, during a fit respiration or aerobic glycolysis probably proceeds at a maximum rate, using up all available oxygen. At the same time the nerve cell increasingly utilizes the relatively wasteful process of fermentation or anaerobic glycolysis as an additional energy source (29a, 52c). Hence lactic acid accumulates in the brain, with a rise in the hydrogen ion concentration (8c, 83). The brain stores of sugar and glycogen diminish (70). Inorganic phosphate piles up due to the eighty times increased utilization of sugar (70). However, aerobic and anaerobic glycolysis are not equal to the task of maintaining a maximally discharging brain. Thus stored energy in the form of phosphocreatine is used up. ATP, the readily-available supply of energy, may or may not remain constant (1a, 24, 41a, 41b, 52c, 70). Gurdjian *et al.* feel that a new steady metabolic state is reached during a convulsion with a high lactic acid and phosphate (41b).

Richter's experiments with frozen rat brains have already been mentioned (24). They show that soon after the start of the convulsion, phosphocreatine, ATP and inorganic phosphate begin to return to normal—even though the convulsion is still in progress. The rats, however, start to breathe at this time. This suggests that the oxygen supply is the limiting factor in high energy phosphate bond resynthesis. Richter feels that this energy is being used to remake the acetylcholine which has been used up by the functioning nerve cells. At any rate, these biochemical findings seem to show that the brain utilizes every available source of energy to the utmost during a convulsion.

Abood and Gerard, however, have some evidence to show that the lowered energy concentration in convulsing brains may be due to decreased synthesis rather than increased utilization (1a, 1b, 39). Indeed, Gerard reports that perfused cat brains can convulse without a rising oxygen uptake and carbohydrate consumption (39). He emphasizes the breakdown of nucleoproteins and lipoproteins which occurs in a convulsion. Apparently this process is reversed by adding nucleic pyrimidines to the perfusion circuit. Since pyrimidines catalyze

phospholipid formation, this finding may relate "fuel to function in brain".

To summarize with regard to the second problem: what happens during a convulsion?

Pathologically, there may be temporary cellular changes following a fit. Physiologically, a convulsion appears to act as a non-specific stress situation. Biochemically, a contradiction exists. On the one hand, a fit seems to increase neuronal metabolism. On the other hand, a fit may depress neuronal metabolism or at least energy synthesis. The point is that none of these effects seems adequate to explain the mechanism of action of EST.

Richter has pointed out that the biochemical events occurring in a convulsion though dramatic are short lived. He postulates that perhaps a change in cell lipoproteins is important (38c). It may be that the most fundamental process which occurs in a convulsion is some sort of change in structure at the intracellular level. Since energy is required not only for impulse transmission but also to maintain cell structure, shifts in energy synthesis or degradation could ultimately affect the organization of the neuron.

Manifestations of such a hypothetical cellular shake-up may be the shifts in ionic concentration, appearance of new substances outside the cell, change in the blood-brain barrier, restorative effect of pyrimidines, changes in cellular appearance, and so forth. Why a convulsion is necessary to produce this change and why it affects the course of the mental disease, are unanswerable questions at present. Indeed, at this level of study, the problem of the mechanism of action of electric shock treatment begins to merge with the problem of the causation of psychoses.

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THE PSYCHOSIS OF ASSOCIATION—FOLIE A DEUX

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The psychosis of association or folie à deux has been defined by Gralnick (9, 10) as a "psychiatric entity characterized by the transference of delusional ideas and/or abnormal behaviour from one person to one or more others who have been in close association with the primarily affected patient."

In 1860, Baillarger, under the title of "folie communiquée", described a case in which two members of the same family were admitted to hospital on the same day suffering from similar delusions. In 1877, Lasègue and Falret coined the neat term "folie à deux" for contagious insanity or the psychosis of association. Within a decade, the primary psychosis had been divided into the following four subgroups:

(a) *Folie imposée* (Lasègue and Falret, 1877).

In the case of folie imposée, the delusions of a psychotic person are transferred to a mentally sound one. The persons concerned have been intimately associated and sheltered from counterbalancing forces. The delusions in the recipient tend to disappear after separation from the inducer.

(b) *Folie simultanée* (Regis, 1880).

In the case of folie simultanée, there simultaneously appears in two morbidly predisposed persons a paranoid, depressive psychosis. Typically, the persons involved have had an intimate and long association.

(c) *Folie communiquée* (Marandon de Montyel, 1881).

In the case of folie communiquée there is contagion of ideas after the second person has resisted them for a long time. After finally adopting the delusions, the recipient maintains them despite separation from the inducer.

(d) *Folie induite* (Lehmann, 1885).

In the case of folie induite, *new* delusions are acquired by one psychotic patient under the influence of another.

Many authorities have attached importance to a supposed "morbid hereditary predisposition" in the psychopathology of folie à deux. Kallmann and Mickey (16) stress the factor of inheritance in consanguineous cases of folie à deux, and suggest that environmental factors are not sufficient in themselves to precipitate a psychosis in family units. Indeed they criticize the whole concept of folie à deux, which they dismiss as "useful for the practice of counting in French, but not for describing the occurrence of similar symptoms in twin pairs or units of blood relatives."

In spite of these strictures many cases of psychoses occurring in consanguineous relatives (including identical twins) have been described as folie à deux. Craike and Slater (7) reported a case of folie à deux in monozygotic twin sisters who shared similar paranoid delusions although they had been separated from the age of nine months. Alder and Magruder (1) described a case of psychosis of association in identical twin sisters which was mainly precipitated as a reaction to environmental complications although there was a constitutional predisposition to schizophrenia. Similarly Oatman (19), in commenting on a case of folie à deux in identical twins, mentions both familial and environmental factors. Finally, Postle (21) reported the case of two sisters who suffered from a psychosis of association of twenty-five years' duration, in which there was a remission in the mental state of the submissive partner following upon the death of her dominant sister who was the inducer of the psychosis. A survey of the literature suggests that, on the whole, most authorities agree that both environmental and hereditary factors play a part in precipitating a psychosis of association even in consanguineous partners, and the highest incidence is found in sister-sister combinations. The present writers suggest that in the case of identical twins the strict application of the diagnostic criteria, to be mentioned later in this paper, will ensure that hereditarily determined non-specific psychoses are not confused with bona fide cases of folie à deux.

Folie à deux very frequently takes the form of a *paranoid* psychosis. The salient features of the *common* paranoid variety are well illustrated in a case reported many years ago by Peterson (20). Two sisters (who were not twins) insidiously developed a psychosis with per-

secutory delusions accompanied by hallucinations of hearing, taste and smell. When first seen, they wore veils, the removal of which revealed that their faces were patched all over with small square pieces of cloth covering sores. An eruption of acne had been made much worse by picking and by their wearing wet clothes all night in order to prevent poisonous vapors from entering their lungs; it was also worsened by the cloths being torn from the bleeding surface. Although persecutory delusions are the rule in folie à deux, religious or grandiose delusions are by no means rare. There are also some cases of folie à deux appearing within the setting of a manic-depressive psychosis.

The authors of the present paper record five cases of folie à deux. There has been no attempt to classify the cases into the usual subgroups, as the authors agree with Brussel (5) and Grover (12) that such treatment is "unnecessary and confusing". Indeed, for reasons which will be advanced later, they doubt the theoretical validity and practical value of these time-honored classifications.

Case 1: Two spinster sisters, aged 74 and 64 years, respectively, who had been living together since the death of their mother 34 years previously, were admitted to hospital in May, 1949, as certified patients. Their doctor's introductory letter stated that they had gradually become more deluded over the past two years, and were now quite incapable of looking after themselves.

The elder sister, Ellen, was the more garrulous. After stating (for no apparent reason) that she and her sister were "virgo intacta", she gave vent to an incessant stream of florid delusions of a persecutory nature. All the domestic misfortunes which had befallen her during the past few months were due, she said, to the machinations of her neighbors' two boys, aged 11 and 15 years, respectively. She alleged that they had stolen her pillow cases, tea cloths and jewelry. In addition, they had removed pins from her brooches and smashed the locks on the doors of her home. Recently, they had entered her bedroom at night and pinched her thighs with such vigor that they were covered in bruises the next morning.

The younger sister, Gladys, harbored similar delusions but expressed them less forcibly than Ellen. She asserted that the two boys had damaged her prayer book and stolen her property. Her speech was slow, and she spoke in a high-pitched, childish voice.

The patients were unkempt in their appearance and wore the garments of an earlier era. They were correctly orientated, but they showed a degree of memory impairment which was more marked in the case of the younger sister. It was evident that the elder sister possessed the more dominant personality, and when they were interviewed *together*, she invariably acted as spokesman. Little information could be obtained about the patients' background. They had been brought up as the only children of a strict, Victorian, middle-class family. Their father had been a solicitor, and their mother had been the headmistress of a village school before her marriage. They owned their own house and had sufficient means for their simple tastes.

The two patients were accommodated in the same ward, where the elder sister continued to play the role of dominant partner, while the younger became more subservient and more feeble. Gladys died six months after admission from bronchopneumonia. Ellen survives (now 80 years old) with her delusional system as florid as on the day of her admission.

Commentary. This is a case of folie à deux in which the elder sister assumed the dominant role. Both the partners were suffering from a paranoid, senile psychosis.

Case 2: A man of Polish nationality, aged 42 years, was admitted to hospital in March, 1954. Immediately prior to his admission, he had received emergency treatment at a general hospital for self-inflicted wounds of the wrists with laceration of the median nerve. This patient (Marian), who could speak very little English, looked depressed, apathetic, and withdrawn. Within 48 hours, his brother (Joseph), aged 46 years, was also admitted in a state of depression and with bilateral wounds of his wrists of a superficial nature. The assessment of the motives of the two brothers was made difficult by the language barrier, as the elder brother had no greater command of English than the younger. At first, it was assumed that the younger brother had, in a fit of depression, lacerated his wrists, and that this had so preyed on the mind of the elder brother that he too had attempted suicide. Accordingly, the brothers were given a course of electroshock therapy with the idea of relieving their depression. It was observed with satisfaction that the treatment resulted in a marked recession in the overt signs of melancholia. Nevertheless, it was noted that whenever one of the brothers was called upon to leave the ward for any reason, the brothers embraced one another with every sign of agitation and despair. In view of this surprising behavior, it was decided to explore the situation further with the help of an interpreter. As a result, the true state of affairs quickly came to light. About a week before their admission, the brothers had become convinced that they were the objects of a campaign of vilification organized by a Lithuanian named Otto, who was one of the inmates of the hostel for foreign workers where they resided. They came to believe that Otto was spreading calumnious stories among the other workers, accusing them of being communist spies. At night, the brothers, who shared a curtained cubicle, thought they could hear Otto successfully proselytizing the other alien workers. One day, on returning from work, they came to the conclusion that their private papers had been searched and scrutinized for evidence of undercover activities. Later, they imagined they could hear Otto debating with the others as to whether they should be handed over to the police, or simply murdered and buried without trace. On the eve of the

wrist-cutting episode, the two men fancied they could hear, through the flimsy curtains of their cubicle, their companions putting the final touches to plans for their liquidation. The next morning, they "heard" the conspirators confer for a few moments, followed by the click of Otto's revolver. It suddenly occurred to the brothers that a lorry, due to call at the hostel for the purpose of removing refuse, might be used to convey them away from the camp at the point of the gun. A moment later, the older man noticed that his brother's wrists were bleeding, whereupon he seized a razor and lacerated his own. The younger man was at once removed to hospital, but his brother continued to conceal his wounds for two days, a task facilated by the fact that they were of a superficial character. Both the brothers denied suicidal intentions (they were Roman Catholics), affirming that they cut their wrists in order to draw the attention of the authorities to their predicament. When taxed with the peculiar behavior that always followed the summoning of one of them from the ward, they explained that this was due to a fear that whoever left the ward was going to his death. However, it was apparent that Marian's fears were more poignant and fixed than those of Joseph. Moreover, when the brothers were interviewed together, it was the younger who did most of the talking. It seemed to be significant that Marian's wounds were deep and grave, whereas those of Joseph were superficial and trivial. The elder brother frankly admitted that his courage had failed him when he felt a spasm of pain on lacerating the skin of his wrists. It was evident that Marian had the stronger personality and was the more intelligent of the two.

Careful enquiries at the hostel showed that Otto was a friendly and harmless individual with an imperfect knowledge of Polish. He possessed a toy revolver which made a clicking sound when cocked. He was completely unaware of the fear he had engendered in the two brothers.

They had suffered the usual hardships and privations meted out to subjects of defeated nations by the German Army of Occupation. After the liberation of Europe, they were housed in a camp for "displaced persons" along with thousands of other refugees. As the Communists had seized power in Poland, the two brothers dared not return to their homeland. Accordingly, they eagerly consented to come to England as volunteer workers. After various adventures, they were eventually accommodated in a hostel for alien workers fifteen miles from the nearest large town. They were now part of a small heterogeneous community of refugees isolated from the indigenous population by their inability to understand English. From time to time, sensational reports appeared in the newspapers describing the mysterious disappearance of prominent Polish émigrés. Such reports produced a wave of anxiety among the Polish refugee population, already rendered uneasy by the paucity of news from Poland. Such conditions greatly facilitated the misinterpretation and paranoid distortion of innocent words and commonplace events.

The electroshock therapy and the friendly atmosphere of the ward exerted so beneficial an effect on the brothers, that it became possible to house them in separate wards. Although separated, they were allowed to see one another for short periods during the day so that neither could think that the other had been executed. Under this regimen, the brothers made a good recovery and were discharged from hospital some seven months after their admission.

Commentary. This is a case of folie à deux initiated, no doubt, by the younger brother. The persecutory delusions displayed by these two "strangers in a strange land" are of special interest in view of a paper by Allers (2) in which he refers to the "persecutory delusions of lingually isolated persons." Kino (17) has also drawn attention to the vulnerability of aliens to paranoid reactions and, like Allers, attributed this to language difficulties. In the case under discussion, it is doubtless of significance that Otto, the evil genius behind the fancied conspiracy, was a Lithuanian with *an imperfect command of Polish.* The writers believe that "lingually isolated" foreigners are in a similar predicament to the deaf, who are notoriously liable to paranoid reactions. Lingually and aurally isolated persons are equally apt to misunderstand and misinterpret innocent remarks, with the development of persecutory ideas.

Case 3: A spinster, aged 49 years, was admitted under certificate to hospital in November, 1947. She asserted that she was the greatest singer in the world, and that the quality of her voice far surpassed that of such renowned singers as Melba and Tetrazinni. She insisted that she could often hear the voice of the late Sir Edward Elgar, and alleged that her name was on books by Elgar and Bach.

This patient's elder sister, a spinster, aged 54 years, was admitted a fortnight later to the same hospital as a certified patient. She was garrulous, elated, and spoke in a rambling fashion of Sir Edward Elgar. She made frequent allusions to the excellence of her younger sister's voice, and stated that she worked diligently at her crochet to help her sister with her singing.

The younger sister, Florrie, persisted in her grandiose system of delusions. Indeed, they tended to become more extravagant with the passage of time. Nevertheless, she remained fully orientated and kept abreast of the times. The elder sister, Lily, continued to share Florrie's system of delusions. She faithfully echoed Florrie's claims concerning Elgar's exalted opinion of her (Florrie's) voice. She too remained fully orientated and abreast of the times. In the ward the two sisters were inseparable. It was noted, however, that Lily adopted a *maternal* attitude towards her younger sister and helped her in many little ways. Thus, she would assist her to dress and wash her back on bathing days.

It was eventually decided to try the effect of housing the sisters in separate wards although they were still allowed to see each other in the presence of a relative on visiting days. The sisters were *separately* interviewed seven years after their admission to hospital, and six months after their accommodation in different wards, with the following result: *Florrie* at once reiterated her grandiose delusions in respect of her ability as a singer. Among other things, she claimed that Elgar had said that "her hair was a glorious colour under the lights, and shone like burnished copper." She also claimed that Elgar had sent her a message that if she "met a shabby old man in the street, it would be Sir Edward Elgar."

When asked how it was that such an incomparable voice had received so little recognition, she asserted that Elgar had spoken of jealousy and compared the attitude of rival singers to that of Othello. *Lily* immediately began to praise Florrie's voice, and to repeat almost word for word the latter's expansive claims. For example, she stated that Elgar had said that Florrie's hair "was a glorious colour in the lights, and shone like burnished copper", and that if she (Florrie) "met a shabby old man in the street, it would be Sir Edward Elgar." Lily also referred to the jealousy of singers less gifted than Florrie and cited Elgar's alleged reference to Othello. It should be made clear that neither sister claimed that Florrie had actually met Elgar *in person*, but both alleged that the younger sister's tutor, a certain Mr. T., had repeatedly informed them of the great Master's admiration for Florrie's voice and comely appearance.

The only advantage gained from the separation was that the younger sister was forced to look after herself instead of allowing her elder sister to do everything for her.

The two sisters had been left to fend for themselves after the death of their mother in 1939 (their father was already dead). There were no surviving siblings. Throughout their life they had been inseparable, and for several years before their admission *they had shared the same bed*. Lily had taken on the role of breadwinner, earning a modest wage as a tailoress in a mill. Florrie spent most of her time at home as she was, in Lily's words, "not for work". At one time, Lily had tried to persuade her sister to train as a shorthand-typist, but Florrie had apparently failed to make the grade. It seems that Florrie had in fact possessed a good voice and had once won a gold medal as a member of a successful choir. Moreover, there was no reason to doubt her statement that she had received a few singing lessons under the tutorship of Mr. T. Nevertheless, her prowess as a singer had been insufficient to command general attention.

Commentary. In this case of folie à deux, it is probable that the younger sister was the architect of the system of grandiose delusions which forms the framework of the sisters' psychosis. Florrie seems to have developed the delusions as an overcompensation for feelings of inferiority engendered by her failure to become a virtuoso singer. On her part, Lily appears to have assuaged her unsatisfied maternal instincts by assuming that role of mother to the younger sister. The delusions of grandeur are a source of gratification to *both* sisters. Lily derives satisfaction from indulging her sister's every whim, much as a doting mother indulges the capricious fancies of a spoiled child. As she listens to the grandiose assertions of her younger sister, her features bear the beatific expression of a mother proudly contemplating the triumphs of a child prodigy. An interesting feature of the case is that the elder sister had no delusions *sui generis*; she merely supported the delusional claims of her sibling.

Soler (22) has described a case of folie à deux involving two middle-aged sisters, the elder having assumed responsibility for the management of the household *on the death of their mother*. The younger grew accustomed to obeying the elder in all matters and to adapting her attitude to the environment. The elder sister ultimately developed delusions of persecution and, subsequently, communicated these to her sibling. The case under discussion is similar to that described by Soler in that the elder sister (Lily) appears to have identified herself with, and assumed the role of, the dead mother; but differs from it in the important respect that the younger sister (Florrie) seems to have acted as the leading spirit and prime mover of the folie à deux. Both patients were considered to be suffering from paraphrenia.

Case 4: Two unmarried sisters, aged 78 and 71 years, respectively, were admitted together to hospital as certified patients in June, 1953. They had caused annoyance to their next-door neighbors by shouting abuse, and had accused these neighbors, a Mr. P and his wife, of entering their house during the night in order to steal money and injure their pet dog. Furthermore, they had accused Mr. and Mrs. P. of conspiring with a former neighbor named K., to enable the latter to continue the campaign of molestation, incitement and persecution by which he had driven the sisters from their previous home. They alleged that K. had been embittered by their refusal to lease him an empty garage attached to their house and, in revenge, had entered their house at night in order to damage their furniture, maim their dog, poison their food, and perpetrate sexual assaults on their persons. In an effort to escape from K.'s malign activities, they had moved to another house only to find that their new neighbors, Mr. and Mrs. P., were in league with K.

The statements of the two sisters were almost identical, but the younger sister, Sarah, admitted that she had never actually seen K. in their house, whereas the elder sister, Hannah, insisted that she *had* seen him there. However, Sarah accepted without question the statements of her sister. It was noted that both the sisters were less adamant and dogmatic in their allegations when *alone*, than when they were in each other's presence. If the conversation was steered away from their specific system of paranoid delusions, they were able to converse in a lucid and coherent manner. Nevertheless, the elder sister displayed a minor degree of memory impairment for both recent and past events.

The sisters were accommodated in the same ward and, for the first few months, continued to denounce "with one voice" the Machiavellian exploits of the villainous K. After some three months, *both* sisters began to show signs of reluctance to discuss their delusions, and to press with increasing insistence for their discharge from hospital. It was obvious that they had come to realize that their allegations against K. constituted an impediment to their release, and that they were making a *combined* effort to hide their delusional beliefs. They now spoke of "forgiving" K. the wrongs he had done them, and of forgetting the past.

They were eventually released eleven months after their admission, having succeeded in *suppressing* their psychosis.

Commentary. It seems probable that the elder sister was the initiator of the psychosis and was the dominant partner. She owed her dominance, no doubt, to her seniority in age. This is a case of folie à deux in which the

older sister displayed a mild, senile psychosis, and the younger sister a paraphrenic psychosis. The paranoid delusions expressed by the two sisters were almost identical.

Case 5: An unmarried woman, aged 42 years, was admitted to hospital in May, 1956, with a paranoid, hallucinatory-delusional system of ideas. She stated that she and her mother had been persecuted for the last three years by her next-door neighbors, who played noisy phonograph records throughout the twenty-four hours of the day in order to cause them annoyance. She alleged that the neighbors on their left played music such as "D'ye Ken John Peel" and "Danny Boy", while those on their right played a recording of a baby's voice. The patient and her mother had repeatedly protested to the neighbors about their unreasonable behavior, yet the persecutions had persisted. Shortly before her admission, she had tried to bring about a cessation of the music by knocking on the bedroom wall, but the music and the baby's crying continued unabated. In desperation she prevailed upon a married-sister to interview the trouble-makers. But the neighbors on the left satisfied the sister that they did not own a phonograph, while those on the right satisfied her that they possessed neither a baby nor a record of its voice. Nevertheless, the patient and her mother were unimpressed by the result of these enquiries, as they continued to hear phonographs being played on both sides of the house. Eventually, the patient began to hear the music *when she was miles away from home*, but even this failed to convince her that her suspicions were ill-founded.

Enquiry revealed the fact that the patient's mother had "heard" the music several months before her daughter. Indeed, she had developed a habit of awakening the latter at night to draw her attention to the music which she believed to be coming from her neighbors' phonograph. At first, the patient had been unable to hear anything unusual on these occasions, but eventually she not only "heard" the music but was able to identify the tune being played. She enjoyed a period of freedom from the music when her mother left home for six months to visit a daughter in Scotland. During the greater part of this time, the patient ceased to hear the phonograph records. However, the music reappeared shortly before her mother was due to return home. The patient's mother "heard" the music during the entire six months of her absence from home, and asserted that it was being relayed to Scotland by the neighbors.

The patient had always been devoted to her mother and very much under her influence. Unlike her six sisters, she had remained unmarried and had dedicated herself to the task of "looking after Mother." Nevertheless, she went out to work during the day. The mother had been a capable woman and was much revered by her daughters. She was described as a "very dominating person with a gift for getting her own way." She certainly had great influence over her daughters, for the married sister who had interviewed the neighbors stated: "If I had stayed a day or two longer with Mother, I too would have heard the music and the baby crying." It is noteworthy that the mother had suffered a stroke paralyzing the right side of her body when she was 78 years old; her hallucinations first appeared some two years later.

A short sojourn (seven weeks) in hospital sufficed to rid the patient of her hallucinatory-delusional psychosis. Before leaving, she was advised to live apart from her mother. The latter had been accommodated in the home of her married daughter, and, as expected, she continued to hear imaginary sounds emitted by imaginary phonograph records.

Commentary. In this case the dominant partner suffered from a senile or arteriopathic psychosis, while the weaker partner developed the rudiments of a paraphrenic psychosis. The hallucinatory-delusional symptoms were identical in the two cases. It is significant that the tunes which the couple thought they could hear would be judged by the present generation as *old-fashioned*. It is also significant that the daughter, who had lost her psychotic symptoms while temporarily separated from her mother, regained them when the return of the latter (from Scotland) became imminent.

Discussion

The authors believe that a diagnosis of folie à deux should not be made unless the following criteria are fulfilled:

(a) The presence of positive evidence that the partners have been intimately associated.

(b) The presence of a high degree of similarity in the general *motif* and delusional content of the partners' psychosis. *N.B.:* The actual *psychosis* affecting the partners may differ, providing the delusions are virtually identical. It is not uncommon to find that one partner has a senile psychosis, while the other had a paraphrenic psychosis.

(c) The presence of unequivocal evidence that the partners accept, support and share each other's delusional ideas.

The commentaries already made on the five cases of folie à deux presented in this paper suggest that each case has specific features in its psychopathology. Nevertheless, there are certain factors that are more or less common to all cases, and which must therefore be accounted of particular significance in the psychopathology of the psychosis of association. *An intimate rapport* between the persons concerned appears to be an essential prerequisite for the development of folie à deux. This intimacy of association is frequently combined with, and facilitated by, an anchoritic attitude towards their fellow creatures: thus, they tend to isolate themselves not only from the community at large but even from their own neighbors. The seclusiveness of these individuals originates, no doubt, from a distrustful

attitude to mankind: a distrust that eventually tends to degenerate into a paranoid psychosis.

This withdrawal from normal social intercourse greatly favors the domination of the weaker partner by the stronger, as the former is thereby cut off from counter-balancing influences. In many cases, there is evidence that a "leader-follower" relationship existed between the partners long before the dominant member became psychotic. It is generally accepted that the phenomenon of hypnosis depends on the establishment of a high degree of dominance by the exponent over the subject. Under these circumstances, the former can induce the latter to accept suggestions without critical appraisal of their validity. A *similar* mechanism would seem to operate in the psychosis of association, the submissive partner being induced *by the process of suggestion* to accept the delusional ideas of the dominant one. Nevertheless, the authors believe that it would be a serious oversimplification of the problem to assume that the psychodynamics of folie à deux are *identical* with those pertaining in the case of hypnotism, as, in the former, the dominant partner's delusions are continually reinforced by a kind of "feed back" mechanism due to the incessant echoing of his beliefs by the weaker member.

What then are the factors which enable one individual to obtain dominance over another? The most important of these are: superiority in age, intelligence, education and "drive" (aggressiveness, etc.). Not rarely, an elder sister materially augments her dominant position (acquired through seniority) vis à vis her siblings by identifying herself with, and replacing, the dead mother (see Soler's (22) case and case 3). Brussel (5) has described an interesting case of folie à deux in which a *partially* blind individual gained dominance over a *totally* blind one, which illustrates *par excellence* the ancient adage: "In the kingdom of the blind, the one-eyed man is King!"

In many cases, the powerful emotional bonds linking partners of the same sex, and the active-passive polarity of their personalities, combine to raise the suspicion that a latent homosexuality may be a factor in the psychopathology of folie à deux. In this connection, it may be significant that the partners not infrequently occupy the same bed.

It is obvious that the factors responsible for the inducer's psychosis may differ in material ways from those responsible for that of the recipient. Griffiin (11) has, for instance, drawn attention to the shock and strain suffered by the (as yet) non-psychotic partner when first witnessing the psychotic affliction of the inducer. It seems reasonable to suppose that the former may be impelled to *identify* himself/herself with the latter as a result of the psychological phenomenon of *sympathy*. Partenheimer, Tuke and Braude (cited by Gralnick (10)) have separately emphasized the role of imitation and/or sympathy in the psychopathology of folie à deux.

Mention must also be made of the psychoanalytical contributions (as represented by Heuyer et al. (15) and Deutsch (8)) to the problem of identification in the psychodynamics of folie á deux. These writers suggest that the delusions of one person will only be taken over by a second person when they provoke in the latter a repressed phantasy life of similar content. Such a phantasy, they suggest, will concern the Oedipus situation, and the inducer will be identified in the mind of the induced with the parent whose place in the original phantasy he takes over. Hartmann and Stengel (13, 14), when commenting on the genesis of a psychosis of association, stress the importance of the inducer's dominance over the induced as an attempt to keep in touch with the exterior world at a time when he feels himself threatened with isolation by loss of contact. Coleman and Last (6) agree with this view, and they also suggest that the following contingencies are essential prerequisites to the development of a psychosis of association: 1) The inducer must be in the early stage of his illness, i.e., before he has become withdrawn from reality. 2) The inducer and induced must be in close proximity to one another. 3) Sharing of the delusion must also be of advantage to the person induced. 4) The inducer must represent authority in the eyes of the induced. 5) The psychosis most commonly develops when persons are living in poverty.

Terminological and Nosological Considerations

The terms "folie imposée" and "folie communiquée" are both used to describe cases of folie à deux in which a dominant individual

implants delusional ideas into the mind of a closely associated weaker one. It is usual to stress the resolution of the weaker partner's psychosis, as a result of separation from the stronger, in cases of folie imposée; a resolution that is supposed not to occur in the case of folie communiquée. However, the authors of this paper suspect that the *duration* of the folie à deux directly influences the stability of the psychosis affecting the weaker partner. For instance, a pair of sisters may develop a psychosis of association which happens to be diagnosed in its early stages. The recipient may then be separated from her partner, and lose her psychosis. In such a case, a diagnosis of folie imposée is likely to be made. But what would have happened if the psychotic partnership had passed unnoticed for many years? The authors believe that under these circumstances the weaker partner's psychosis would ultimately become fixed, thus satisfying the criteria for a diagnosis of folie communiquée. In short, folie imposée would have become folie communiquée simply as a result of the proconged duration of the psychosis. The view that the *duration* of the folie à deux is directly related to the fixity of the recipient's delusions receives support from a statement by Gralnick (10): "The length of association after the onset of psychosis in the recipient is also important. The longer this association, the poorer the prognosis." The authors therefore believe that there can be no essential difference between folie imposée and folie communiquée.

In any case, the stability of the psychosis affecting the weaker partner probably depends not only on the *duration* of the psychosis, but on the *nature* of the delusions. If these are of value to the weaker partner (by satisfying a psychological need), he/she will cling tenaciously to the psychosis. Moreover, the stability of the weaker partner's psychosis also depends to some extent on her *suggestibility*. A person highly vulnerable to suggestion can acquire delusional ideas with great speed and facility; but such ideas are unstable as they are easily displaced by counter-suggestions. A less suggestible individual will take longer to acquire such delusional ideas but will doubtless hold them with greater persistence.

The presence or absence of these variables (duration of the psychosis, nature of the delusions, and suggestibility of the weaker partner) hardly justifies the differentiation of a "folie imposée" from a "folie communiquée".

The term "folie simultanée" is completely insupportable as it is inconceivable that two intimately associated persons have not influenced one another, should they suddenly develop an identical set of dilusions. If it is accepted that they *have* influenced one another (and the definition of folie à deux requires that this is so), then it transcends the bounds of probability to suppose that the partners did so *simultaneously*. It is virtually certain that one partner developed the delusions first (no matter how short the time interval) and *thereafter* transferred the delusions to the other.

The term "folie induite" is entirely redundant and merely complicates the existing terminology. The development of an additional group of delusions by one psychotic patient as the direct result of the influence of a more dominant companion involves the operation of precisely the same mechanisms as when this phenomenon concerns a dominant, psychotic partner and a submissive, normal one.

Quite apart from any theoretical objections to their use, the classical sub-groups are of scant practical value. For instance, it is often impossible to identify with certainty the dominant partner or to assess the duration of the primary and secondary psychoses.

There is some division of opinion regarding the concept of contageous insanity on the grand scale. Brussel (5) coined the term "folie à beaucoup" in such cases, but the present writers object to the use of this phrase which has no idiomatic meaning in French. As an alternative they suggest the term "folie collective". But an alternative expression does not lend substance to a clinical entity which many psychiatrists maintain does *not* exist. Oatman (19), for example, maintains that a term such as "folie collective" cannot be properly applied to a large group such as "those who absorb the religious or pseudo-philosophic delusions of their self-appointed leaders, such as Joan of Arc and Father Divine." Nevertheless, Bender and Yarrell (3) presented the case histories of 18 psychotic disciples of Father Divine who were all admitted to the same mental hospital with similar delusions. Although Bender and Yarrell did not describe their cases as "folie collective", their case reports are highly suggestive of contagious in-

sanity. More convincing evidence comes from Minovici (18). He described, under the title of "folie communiquée" a family suicide involving 10 people, which in our opinion is an example of "folie collective". Gralnick (9, 10) also criticized Brussel's concept of contagious insanity on the grand scale, and he effectively dismissed some of the more dubious examples such as "The Charge of the Light Brigade" and "Joan of Arc". The present writers (although disagreeing with Brussel's terminology) feel that there is some substance in his contention that a psychosis of association may involve a large number of people. The following historical example is difficult to explain in other terms (4).

In 1838, a madman bearing the assumed title of Sir William Percy Honeywood Cortenay, Knight of Malta, led a series of remarkable riots at Bossenden Wood in England. This man, who had previously spent some years in a lunatic asylum, wore on his chin a magnificent coal-black beard and was attired in a theatrical-looking tunic, upon the breast of which the Maltese Cross was embroidered in golden wire; while the ample folds of a cloak of Tyrian blue were draped around his shoulders. It appears that (in the words of the narrator) "his insane spirit communicated itself to the rustics" since they came to share his belief that he was the "Son of God". Many of the yokels who flocked to his side sank down on their knees and openly worshipped him. After perpetrating the cold-blooded murder of a constable sent to apprehend two of his followers, he marched a troop of his disciples to Bossenden Wood where among other mad antics, he administered the sacrament in bread and water. Shortly after this, he was killed with many of his men in a bloody encounter with armed soldiers sent to effect his arrest.

The luckless followers of this flamboyantly dressed madman appear to have had no other motive for their actions than an unshakable belief in the delusional ideas of their colorful leader.

Summary

This paper has been divided into three parts:

The first part includes Gralnick's concise definition of folie à deux. In addition, it contains a brief historical review of the disorder and its classical subgroups. Lastly, it embodies a summary of its cardinal features.

The second part consists in a descriptive of five new cases of folie à deux.

The third part contains a list of criteria which the authors believe must be fulfilled before a diagnosis of folie à deux can be made. The psychopathology of folie à deux is discussed, and the validity and usefulness of the classical subgroups challenged.

Finally, the authors support Brussel's concept of a "folie à beaucoup", which they prefer to call "folie collective".

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SOME RECURRENT LIFE HISTORY PATTERNS OBSERVED IN PATIENTS WITH MALIGNANT DISEASE[1]

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INTRODUCTION

The possibility that there may be personality factors or life history patterns which correlate highly with the appearance of neoplastic disease has received increasing attention in the past five years. Two recent reviews of the literature (8, 11) have pointed out that this concept was advanced by many physicians in the 18th and 19th centuries. At the end of the 19th century (possibly due to the fact that there were no available tools to develop it further, and that a very real promise was held out by surgery and radiation), the idea largely disappeared from the medical literature. Only occasional publications discussed it until 1952 when the paper of Tarlau and Smalheiser appeared (14). Since that time, an ever increasing number of studies in this area have been appearing in the literature.

This report is based on a study of 250 individuals with malignant disease whose personalities were evaluated by means of a projective test, the Worthington Personal History. In addition, exploratory clinical interviews were given to 80 of these patients. Seventy-one of these were seen for either two or three hours. Nine patients were evaluated more intensely for a total of 1,070 hours of interviews. In this report we will attempt to summarize the psychological patterns that appeared.

METHODOLOGY

The Worthington Personal History is a projective device constructed in the form of a life history questionnaire. It has been administered to over 12,000 individuals, most of them with no known disease. Reports in various publications (i.e., 13, 15) have indicated its high degree of validity when used by clinicians competently trained.

The 250 patients studied by means of this test were all under treatment for malignant neoplasms. Table 1 shows the locations of the tumors.

In order to be able to test hypotheses which were arrived at in the analysis of the projective test protocols, and to develop new hypotheses, a program of interviewing patients was initiated. Seventy-one of the patients tested received between 1½ and 3 hours of clinical interviewing. An average of 2.2 hours was spent with each patient in this group.

As a third method of testing and developing hypotheses, nine patients with malignant neoplasms were seen in more extensive series of interviews. The number of hours each of these nine patients received in this clinical exploration is shown in table 2. All nine patients knew their diagnosis and the usual prognosis for their type of illness.

Personal History forms were also obtained on an age-equated group of 150 individuals with no known disease (15 of these control subjects also were given at least a one-hour clinical interview). The psychodynamic arrays of personality organization observed on over 12,000 essentially normal cases were congruent with those found in this control group.

The projective tests and clinical interviews obtained on the patients with malignant neoplasms seemed to the writers to indicate a consistent life history pattern.

FINDINGS

In the analysis of the protocols of the projective tests and interviews, four factors appeared to be characteristic of the cancer patients and not of the controls. These were:

1. The loss of a major relationship prior to the first observed signs of the tumor and a failure to establish a satisfactory substitute cathexis. In the relationship that was lost, these patients had been able to express their vitality and emotional energy easily and with feelings of reward and satisfaction. In other and in succeeding relationships, they have been unable to do this.

[1] This research was done under the auspices of a grant from the Ayer Foundation, Inc.

2. A blockage in their ability to express hostile feelings and, very frequently, the presentation of a social façade of benign goodness and kindness. They often could express aggression or hostility in the defense of other people or of ideals, but found great difficulty in expressing feelings of anger in defense of themselves.

3. A marked amount of self-dislike and self-distrust. These individuals do not approve of themselves or believe themselves to be worthy individuals.

4. Tension over the relationship with one or both parents. This appeared in particularly sharp focus when one of the parents had died. Often this death had occurred far in the past, but evidence of strong unresolved tensions in this area was still present.

A. The loss of a major relationship

Seventy-seven per cent of the experimental subjects and 14 per cent of the controls showed marked tension over the loss of a vital relationship. Most frequently, this occurred in the family area and concerned a spouse or children (61% of the records). Less frequently, an occupational loss was involved, or the loss of peer group relationships (15% of the records).

These patients appeared, from the protocols, to be individuals who had difficulty initially in establishing a major relationship and who, when they did achieve a satisfactory one, poured a major portion of their life energy into it, remaining somewhat barren and superficial in other spheres. Insofar as could be told from our data, the loss antedated the appearance of the tumor from between 6 months to 8 years. In some cases, such as the loss of parental relationships with children who were growing up and becoming independent, it was not possible to establish clearly a time of loss although test responses indicated that the loss was felt keenly by the subject.

B. The inability to express hostile feelings

Sixty-four per cent of the experimental subjects and 32 per cent of the control subjects indicated in the test protocols an inhibition of hostility: a psychological inability to express anger, resentment or aggression toward other people although they could epress these feelings in the defense of other people or of ideals.

TABLE 1.—PATIENTS WITH MALIGNANT DISEASE TESTED

Primary Site or Type of Malignancy	Number of Patients
Breast	55
Skin	21
Colon	20
Hodgkin's Disease	20
Rectum	17
Lung	17
Buccal area	13
Stomach	10
Cervix	9
Prostate	10
Thyroid	6
Uterus	6
Lymphosarcoma	6
Ovary	4
Miscellaneous	18
Primary uncertain	18
Total	250

TABLE 2

Number	Location of Tumor	Sex	Age	Interview Hours
1	Lung	M	44	283
2	Hodgkin's Disease	F	33	207
3	Sarcoma of leg	F	34	190
4	Melanoma	M	33	120
5	Lung	M	54	70
6	Breast	F	32	64
7	Stomach	F	62	41
8	Hodgkin's Disease	M	36	50
9	Hodgkin's Disease	F	36	49
Total				1,074

C. Self-dislike and self-distrust

Seventy-nine per cent of the neoplastic patients and 34 per cent of the controls indicated a strong sense of personal unworthiness and culpability.

D. Tension concerning the relationship with one one or both parents

Thirty-eight per cent of the experimental group and 12 per cent of the control group demonstrated unusual tensions in this area. In some cases, a parental death had occurred as much as 30 to 40 years in the past, but guilt and anxiety concerning this event and the relationship were still present.

TABLE 3.—FACTORS FOUND DIFFERENTIATING EXPERIMENTAL AND CONTROL SUBJETS

Factor	Patients with Malignant Neoplasms: N = 250		Control Subjects (No Known Disease): N = 150	
	Number	Per cent	Number	Per cent
1. Loss of a major relationship before first observed symptoms of cancer	192	77	21	14
2. Difficulty in expressing hostile feelings	159	64	48	32
3. Marked self-dislike	198	79	51	34
4. Tension over the relationship with one or both parents	108	43	18	12

DISCUSSION

1. *The loss of a major relationship.* This factor has been reported by other observers (4, 5, 6). It has also been demonstrated that it is possible to use this factor to predict relative cancer mortality rates of different social groups and that these predictions can be validated by use of the published cancer statistics (10).

2. *The inability to express hostile emotions.* The association of this factor with cancer has been previously reported by Cobb (3), Bacon, Rennecker and Cutler (1), and by Butler (2). From these studies, however, it has been very difficult to ascertain if this characteristic existed prior to the appearance of the cancerous condition. From the projective test protocols gathered in the present study, it is also impossible to be certain. Nevertheless the interviews clearly indicate that the inability to express aggression has been a life-long pattern antedating the appearance of the tumor.

One aspect in which our findings and previous studies differ is that they have reported a *general* inhibition of hostile feelings. The data evaluated here clearly point to a *specific* inhibition—an inability to express aggressive feelings in defense of oneself, but greater ease in expressing these feelings in defense of others or of social ideals.

3. *Self-dislike and self-hatred.* This factor has been implicitly noted by Evans (4). It may well be that the finding of a "masochistic character structure" made by Bacon, Rennecker and Cutler (1) on their patients with breast cancer is a statement about the same data we are reporting.

4. *Tension over the death of a parent.* Strong unresolved tensions concerning parental figures have been previously reported although these reports do not discuss the significance of this factor in relation to the death of a parent. This has been noted by Evans (4), Tarlau and Smalheiser (14), and Bacon, Rennecker and Cutler (1). These reports appear to be in essential agreement with our findings. Tension in relating to a parental figure leads frequently to unresolved problems of guilt and anxiety after the parent's death.

In the analyses of projective material (as in the analyses of interview data), underlying psychodynamic patterns and energy complexes are hypothesized. In our evaluation of the protocols we have obtained in this study, we have noted repeatedly (in 62% of our cases) a general psychological pattern which appears to link our three observed factors together. In earlier studies of such diseases as peptic ulcer, asthma and ulcerative colitis, it was of help to many investigators to have reports on the psychodynamic life history patterns of individual patients, whether or not these became specific to the particular disease in large scale, statistical terms. In view of this, we feel it is valid to report on the following observations. The pattern we observed so frequently was as follows:

Sometime in the first seven years of life, there was a trauma to the child's developing ability to relate to others. This trauma may have come from a variety of causes—the physical or psychological loss of a parent, the death of a sibling, or others.[2] This trauma was related by the child to one or both of the parents, and a great deal of hostility resulted. However, the hostility could not be consciously accepted by the child for obvious reasons, and it was repressed. A large part of it was turned inward as self-hate and guilt feelings. In addition, the ability to express emotion in relating to others was severely damaged, and the child experienced unusual difficulty in establishing strong cathexes of either a positive or negative nature.

The ability to express positive emotions

[2] Reznikoff (12) in a careful study of women with breast cancer has reported that the death of a sibling during the patient's childhood was a factor which clearly and statistically differentiated his patients with malignant neoplasms from his control groups.

was weakened by the pain of withdrawing love from the parental figure. Negative feelings were hard to express due to the strong, unacceptable hostility also directed in this direction. Guilt feelings over the relationship with the parents tended to produce feelings of unworthiness.

The trauma producing these results was not of an intensity or timing likely to produce obvious neurotic problems or to prepare the person for a psychotic breakdown in the event of later stress. Although it made his later relationships generally superficial and invested in only cautiously, from a surface viewpoint, he managed to adjust to his social environment.

The personality development before the trauma was such that the individual had a need for warm relationships. As he developed and continued to have this need for, but inability to attain easily, warm cathexes, sooner or later a situation arose which offered him an opportunity to relate to others and which provided time for slow and cautious experimentation. This experimentation indicated that this was a "safe" relationship, one that would give him the warmth he needed, and would not mobilize the repressed hostile feelings.

The cathexis was accepted, and the person poured into it all the relationship needs that he had carried over the years since the original trauma. This tie became the focus of his life and all other relationships were essentially peripheral to it. The self-hatred was largely dissipated as the energy that once fed it was now rechanneled. Life-long patterns and basic guilt feelings, however, frequently still made it difficult for the person to express hostile feelings when his own needs were frustrated.

Eventually this cathexis was lost. This may have been due to any one of a number of events. The examples we have most frequently seen include the death of a spouse, or an event which markedly changed the marital roles, such as the chronic illness of a spouse; children growing up and attaining independence, thereby making parental roles obsolete; and job retirement. The self-hate was now rearoused as the blocked relationship energy turned inward through the old channels and was again expressed against the self. The loss of this all-important cathexis made it very difficult for the individual to relate again to others. He unconsciously saw what was happening as a "double desertion". The unconscious belief that to relate meaningfully to anyone brings the pain of desertion was reinforced by the second loss. The child's belief that he was responsible for the rejection was again accepted, and guilt and self-hate were again strongly felt.

This psychodynamic pattern was observed in 62 per cent of our neoplastic cases and in 10 per cent of our controls. Following are a few case histories, briefly described, indicating some of the ways in which this basic pattern seemed to operate:

Case 1: A 54-year-old male with lung cancer. He experienced a warm family life for the first four years. Then his father deserted the home. He felt hostile toward him and guilty over this reaction. Lacking feelings of support, he sublimated through work, first in school and later in the business world. He gained a kind of security from material success, but always felt that something was lacking in his life. His relationships with others were superficial. He achieved a very high level of occupational success through unusual drive and ambition. At 49, he was offered a job by an easygoing, kindly man. He saw this man as "being the balance I'd always needed." He became a friend and follower of this man and, in so doing, suppressed his own initiative and drive. Gradually, he realized that his superior was, in reality, somewhat inefficient and undependable. He felt blocked and lost. He rationalized his immobilization and stayed on the job; his energy output was considerably lowered and blocked. For years he had been working very hard; now he was unable to do anything but the most routine tasks. He felt extremely hostile towards his superior, but did not overtly express this. The interest he had always put into his work disappeared, and he no longer had an outlet for his energy and drive. This condition continued for two years before the lung cancer appeared.

Case 2: A 60-year-old female with breast cancer. As a young child, she was much loved and protected in a warm European home. In her seventh year, the father left home to come to America. He took the older children with him, and the family was split for several years. She felt marked hostility toward her father for this, but it was repressed. In the face of the loss of support, she changed her role and became an "assistant mother", thereby denying her own need for protection. As a life pattern, she has denied her hostile feelings, finding "some good in everyone." She later married a weak and somewhat inadequate male and spent her life taking care of him and their four children. She worked very hard at this. As one of the children expressed it, "When J. broke his leg, she carried him on her back to school." (This is apparently a literal account from the viewpoint of the children and the woman herself.)

All four children went into fields demanding high intellectual activity and were successful at them. The husband died after 15 years of marriage. She continued

her usual behavior of taking care of her children and investing all her time and energy in them. She led a happy life in spite of economic pressures until the youngest child grew up and went to work. She went to live with him and, as his work took him to various towns for assignments ranging from a year to three years, she also went from town to town, cooking and keeping house for him. Finally it became clear that he no longer needed her and would be happier without her. She felt confused and unhappy. She considered various occupations and hobbies, but could not become really interested in any of them. For a time she did very little of anything. She became more quiet and relaxed than the children had ever seen her before. About one year after she stopped keeping house for the youngest child, the breast cancer developed.

Case 3: A 28-year-old female with adenocarcinoma of the thyroid. As a child she was close to both parents, but particularly to her father. He died when she was three years old. Her test protocols still show marked tension over this loss, and the tension is also shown by her statements during the interviews. She lived with her mother and older sister in a small town. When she was 15, the sister died of nephritis. She and the mother were both "upset", and the patient went to a large nearby city to stay with friends for six months "until we all got over it." This was during World War II, and the friends who ran a hotel badly needed assistance. The patient began to work there and enjoyed the work. "I love to meet and talk to people and there were a lot of people there." Her future husband came there as a guest, and they met. He is a theoretical scientist and is 18 years older than she. They courted and "had a wonderful time. Theater, weekends, we had a boat on the lake," etc. After they were married, they were happy for a time. Then his interest in his work grew stronger and stronger. She found she could not understand what he was thinking about, and his conversation often baffled her. She had to hold herself back from him, from being too loving and demonstrative or "he would get so involved in his work, he'd work until 11 or 12 at night at the laboratory." She loved parties, and he did not. When they went to one, "he sits in the corner with a long face, thinking about his experiments." After one or two days of vacation, "he starts to jot down notes for a new paper he's going to write." His interest in music and art was far from hers, but she saw to it that he indulged his tastes because she wanted him to be happy. She markedly inhibited her expressions of hostility and apparently has done this for many years. The cancer developed five years after her marriage.

Case 4: A 60-year-old male with cancer of the prostate. When he was 8 years old, a younger (six-year-old) sister died in an accident. They had apparently been quite close, and in this particular family constellation, it was an unusually devastating blow. He felt let down by his parents as he had not believed they could or would let such a thing happen. His hostility toward them also produced guilt feelings. At the time of the accident, he still viewed his parents as being perfect and powerful, more so than other people. The demonstration of their lack of ability to protect his sister and him in all situations was a shock to him.

Superficially, he adjusted well until his marriage in his late 20's. He had no close friends and never became emotionally involved with anyone until he met his future wife. They came to know each other very well over a period of three years, and fell deeply in love. The marriage was a close and a good one. There were children, but his wife was always the focus of his relationship energies. They were always together except when he was at work, and they discussed his work in the evenings. She died when he was 56. He felt terribly isolated and lost interest in his work. He still liked seeing his children and grandchildren, but there appeared to be little emotional intensity on his part in these relationships. He kept his job but, for the first time, felt bored by it. The prostate cancer appeared when he was 59.

Case 5: A 36-year-old female with carcinoma of the breast. She was very much loved and was given much warmth by her parents for the first four years of her life. In the course of psychotherapeutic exploration, she recalled this period as full of "golden moments". The father was a man who was very dependent upon his business success for his feeling of security, and when she was four years old, he suffered a series of financial reverses. He became somewhat morose and much less interested in his family. She felt rejected, and her developing Oedipal relationship became filled with hostility and guilt. She did fairly well in school and college, but never developed any close relationships nor trusted other people. At the age of 30, she became engaged to a much older man (whom she did not love) because her mother very strongly approved the marriage. She put off the marriage for several years until her mother became ill and died. A few months later, she married him. He was stationed at a Naval base, and for a year this marriage was an extremely happy one. She took a job on the base, and they were very close, sharing interests in their work and enjoying exploring the surrounding countryside in their free time. At the end of the year, he was transferred to sea duty and was away for nearly two years. After he returned, the relationship changed markedly.

In the Navy, her husband had been cut off from his only real interest—his business, and had therefore shared much of his energy with her. Back in civilian life, he found the business taking more and more of his thoughts and time as it had done before he entered the Service. She felt more and more alone and left out of his life. She perceived she had married a man very similar to her father. She felt they were interested in different things, liked different people, and had different approaches to everything. "He can't understand what I like. All he is interested in is his business, and it bores me to listen to him tell me about it. He is just like my father. All he is interested in is his store." The three children gave her no satisfaction; she wanted to love them but was unable to. She did not consider divorce but would have agreed had her husband raised the question. In disagreements, she would never argue or get angry, but would passively accept the viewpoint of her opponent. In sexual relationships, if she wished to reach a climax, she had to close her eyes and imagine she was with someone other than her husband, but she could never perceive who this other person was.

Seven years after the marriage, an extremely anaplastic breast carcinoma developed.

Summary

In the clinical evaluation of 250 patients with malignant neoplastic disease, four factors were found which appeared to differentiate them from a control group. These were: 1) a lost relationship prior to the diagnosis of the cancer; 2) an inability to express hostility in their own defense; 3) feelings of unworthiness and self-dislike; 4) tension over the relationship with one or both parents.

A psychodynamic pattern emphasizing a traumatic event in childhood and including the factors listed above was hypothesized for 62 per cent of the neoplastic patients and 10 per cent of a control group.

Although the writers take full responsibility for this paper, it is a pleasure to thank the individuals who have made this study possible. They include Marthe Gassman, M.D., who acted as control therapist for the intensive interviews and as psychiatric consultant to the study; Robert A. Ravich, M.D., and Emanuel Revici, M.D., respectively Clinical Director and Scientific Director of the Institute of Applied Biology, who were medical consultants. We owe much to their perception and encouragement.

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EFFECTS OF PSYCHOTOMIMETIC COMPOUNDS ON CERTAIN OXIDATIVE AND HYDROLYTIC ENZYMES IN MAMMALIAN BRAIN[1,2]

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Among the ever-growing list of compounds which profoundly alter human behavior, mescaline remains of great interest partly because of the many structural analogs which may be synthesized. Analysis of the effects which mescaline and its isomers produce at a molecular, cellular, and psychic level (8) may provide insight as to the mechanism of action of the psychotomimetic drugs. As yet, the unique psychic effects of mescaline are not shared in a known way by a comparably unique effect on a cellular system. To date, the enzymatic approach has not provided information of value in understanding the activity of the psychotogens (1). Nonetheless, study of the relation between structure and enzymatic activity may suggest means by which structural antagonists may be prepared, means by which brain cells may be temporarily or permanently damaged, and perhaps someday, to help in understanding the relationship between mental disease and cellular metabolism. The work reported here is an extension of research (9) dealing with the direct effect of these compounds on enzyme systems *in vitro*.

Methods and Materials

A tissue preparation consisting of the cerebrum and underlying structures from the rat brain was used as the source of enzymes in this study. This tissue was homogenized with distilled water in an all-glass homogenizer followed by dilution appropriate for optimal measurement of the individual enzymes.

Partially purified alkaline phosphatase (AP), prepared by the method of Morton (13) was used in one phase of this study.

Alkaline phosphatase activity was measured in brain homogenates, supernatants from brain homogenates and partially purified brain alkaline phosphatase preparations. The method employed was that of Bessey, Lowry and Brock (7) as modified by Lowry *et al.* (12) for brain tissue, using p-nitrophenylphosphate as substrate and either glycine (.05 M) or 2-amino-2-methyl-1-propanol (AMP) (1.0 M) as buffer. The rate of tissue respiration utilizing pyruvate as substrate was measured by the method of Elliott *et al.* (10). For ease of discussion, the oxygen consumption measured this way is referred to in the text as "pyruvate utilization". Lactic and malic dehydrogenases (LDH and MDH) were determined by the spectrophotometric method of Strominger and Lowry (17).

Compounds to be tested were added to the various reaction mixtures by dissolving or suspending them in the buffer component, with pH readjustment where necessary. Special controls were run for compounds which produced color in the reaction mixture. In some instances, the insolubility or color development of a compound limited the concentration which could be used. All compound concentrations are expressed as the molarity existing in the reaction mixture during the period of incubation. Most of the primary β-phenethylamines and many of their analogs were prepared especially for use in this study (2–6). All the amines were used as hydrochlorides or in a few cases as the sulfate.

Results

Alkaline phosphatase and substituted phenethylamines

Typical pH curves for brain AP activity are shown in figure 1, illustrating the difference in activity attainable when two different buffers were used. Maximal activity in the glycine-buffer system was only 54 per cent of that found using 0.1 M AMP buffer. In a 1.0 M

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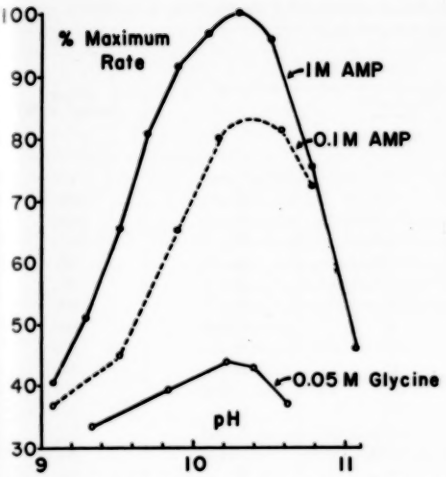


FIG. 1. A comparison of the relative effects of glycine and AMP buffers on brain alkaline phosphatase activity as influenced by pH. See text for details of enzyme reaction.

TABLE 1.—RELATION OF BRAIN ALKALINE PHOSPHATASE ACTIVITY TO CONCENTRATION OF 2-AMINO-2-METHYL-1-PROPANOL BUFFER

Buffer Concentration	Relative Enzyme Activity
(M)	
0.05	62.4
0.125	83.4
0.25	84.5
0.50	93.6
0.75	94.0
1.0	100.0

Reaction mixture: disodium p-nitrophenylphosphate (8 mM); $MgCl_2$ (2 mM); buffer, pH 10.4, as indicated above; brain homogenate to provide less than 4% hydrolysis of substrate during incubation at 37°C. for 30 minutes.

AMP buffer the enzyme activity was further increased. Similar pH curves were found for human serum AP activity. The quantitative relationship between AMP buffer concentration and AP activity is shown in table 1.

The fact that this enzyme shows very high activity in an amine buffer has special significance since it adds weight to the specificity of the inhibitions caused by the compounds being tested, most of which are cyclic amines present in a concentration $\frac{1}{100}$th that of the amine buffer used. It can be seen from table 2 that there was good agreement between the effects of the test compounds on AP activity in glycine and AMP buffer.

A series of 19 β-phenethylamines, including mescaline, was tested for effects on AP activity in order to study the relationship between structure and influence on enzyme activity. From this study (table 3) it is apparent that the *position* of substitution on the ring was more important than the *nature* of the substituent although the latter did exert some influence. In general, compounds which had substitutions in the 3,4,5 positions had only slight effects on the activity of the enzyme, whereas the unsubstituted compound, phenethylamine, exerted a definite inhibition.

Compounds having both the 2 and 6 positions alkyl- or alkoxy-substituted were more inhibitory to the enzyme than 3,4,5-substituted amines. Where the substitution was asymmetrical as in the 3-methoxy and the 2,3-methoxy compounds, there was also a fair degree of inhibitory action.

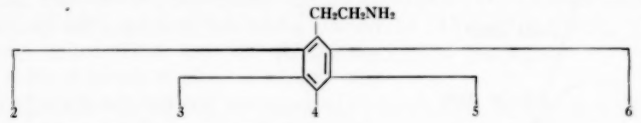
From an examination of 2,4,6-substituted compounds, it would appear that the degree of inhibitory effect was related to the nature

TABLE 2.—COMPARISON OF THE EFFECT OF COMPOUNDS ON BRAIN ALKALINE PHOSPHATASE ACTIVITY IN GLYCINE AND 2-AMINO-2-METHYL-1-PROPANOL (AMP) BUFFERS

Compound (10 mM)	Enzyme Activity (control = 100)					
	Glycine*			AMP†		
	N	Range	Mean	N	Range	Mean
Bufotenin	7	120–139	128	2	119–121	120
Serotonin	3	76–91	81	2	70–74	72
d-LSD-25	—	—	—	5	100–127	112
Mescaline	3	92–95	94	7	92–100	97

Reaction mixture as described in table 1.
* 0.05 M in reaction mixture.
† 1.0 M in reaction mixture.

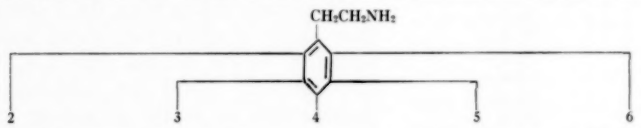
TABLE 3.—Effect of Phenethylamines* on Brain Alkaline Phosphatase Activity†



2	3	4	5	6	Activity (control = 100)
CH_3O	CH_3O	CH_3O	CH_3O	H	106
H	CH_3O	C_2H_5O	CH_3O	H	105
H	C_2H_5O	C_2H_5O	CH_3O	H	101
H	CH_3O	OH	CH_3O	H	97
H	CH_3O	CH_3O	CH_3O	H	97
H	CH_3O	CH_3O	H	H	90
CH_3O	CH_3O	CH_3O	H	CH_3O	90
H	H	H	H	H	89
H	CH_3O	OH	H	H	88
CH_3O	H	CH_3O	H	CH_3O	88
H	H	OH	H	H	87
CH_3O	CH_3O	H	CH_3O	CH_3O	86
CH_3	CH_3O	CH_3	CH_3	CH_3O	83
H	CH_3O	H	H	H	81
CH_3O	CH_3O	CH_3O	CH_3O	CH_3O	81
CH_3O	CH_3O	H	H	H	80
C_2H_5	H	C_2H_5	H	C_2H_5	77
C_2H_5O	H	C_2H_5O	H	C_2H_5O	57
CH_3	H	CH_3	H	CH_3	46

* 10 mM concentration of phenethylamines in reaction mixture.
† Reaction mixture as described in table 1 using 1.0 M AMP buffer.

TABLE 4.—Effect of Phenethylamines* on Brain Respiration using Pyruvate Substrate†



2	3	4	5	6	Activity (control = 100)
H	CH_3O	OH	H	H	76
H	H	OH	H	H	76
H	H	H	H	H	72
CH_3O	CH_3O	H	H	H	69
H	CH_3O	H	H	H	63
H	CH_3O	OH	CH_3O	H	63
H	CH_3O	CH_3O	H	H	61
CH_3O	CH_3O	H	CH_3O	CH_3O	61
H	CH_3O	CH_3O	CH_3O	H	58
CH_3O	CH_3O	CH_3O	CH_3O	CH_3O	50
CH_3O	H	CH_3O	H	CH_3O	47
CH_3O	CH_3O	CH_3O	H	CH_3O	45
H	CH_3O	C_2H_5O	CH_3O	H	29
H	C_2H_5O	C_2H_5O	CH_3O	H	24
C_2H_5O	H	C_2H_5O	H	C_2H_5O	10
CH_3	CH_3O	CH_3	CH_3	CH_3O	9
CH_3	H	CH_3	H	CH_3	9
C_2H_5	H	C_2H_5	H	C_2H_5	5

* 10 mM concentration of phenethylamines in reaction mixture.
† Reaction mixture: 200 mg. brain; sodium pyruvate (.02 M); balanced salt solution to 3.0 ml.; pH 7.35, 37.5°C. for 1 hour.

TABLE 5.—EFFECT OF CERTAIN ANALOGS OF PHENETHYLAMINES ON BRAIN ALKALINE PHOSPHATASE ACTIVITY AND PYRUVATE UTILIZATION

Comp. No.	Compound*	Alkaline Phosphatase	Pyruvate Utilization
		(control = 100)	
1	benzylamine	78	81
2	phenethylamine	89	72
3	phenylisopropylamine (Dexedrine)	95	71
4	N,N-dimethylphenethylamine	106	88
5	N-methylphenylisopropylamine	100	71
6	N-methylcyclohexylisopropylamine (Benzedrex)	101	24
7	N-methylphenylisobutylamine (Wyamine)	117	61
8	benzoic acid	103	101
9	phenylacetic acid	103	95
10	benzamide	98	78
11	phenylacetamide	104	71
12	4-hydroxyphenethylamine	87	76
13	4-hydroxycyclohexylethylamine	86	53
14	4-methoxybenzylamine	66	75
15	4-methoxyphenylisopropylamine	74	61
16	3-amino-1-(4 methoxyphenyl)butane	63	27
17	N-benzyl-4-methoxyphenylisopropylamine	110	8
18	4-hydroxy-3-methoxyphenethylamine	88	76
19	4-hydroxy-3-methoxycyclohexylethylamine	96	70
20	3,4-dimethoxyphenethylamine	90	61
21	3,4-dimethoxyphenylisopropylamine	96	56
22	N-benzyl-3,4-dimethoxyphenylisopropylamine	97	11
23	N,N-dimethyl-3,4-dimethoxyphenethylamine	92	—
24	3,4-dimethoxyphenylacetic acid	107	102
25	3,4-dimethoxyphenylacetamide	104	78
26	3,4,5-trimethoxyphenethylamine	97	58
27	3,4,5-trimethoxyphenylisopropylamine	101	50
28	N-methyl-3,4,5-trimethoxyphenethylamine	105	64
29	N,N-dimethyl-3,4,5-trimethoxyphenethylamine	102	—
30	3,4,5-trimethoxybenzoic acid	104	74
31	3,4,5-trimethoxybenzamide	104	51
32	2,4,6-trimethoxyphenethylamine	88	47
33	2,4,6-trimethoxyphenylisopropylamine	90	28
34	2,4,6-trimethylphenethylamine	46	9
35	2,4,6-trimethylphenylacetic acid	101	72
36	2,4,6-trimethylphenylacetamide	114	49
37	N,N-diethyl-2,4,6-trimethylphenylacetamide	104	36

Reaction mixtures as described in tables 3 and 4.
* 10 mM concentration in reaction mixture.

of the substituent group as follows: $CH_3 > C_2H_5O > C_2H_5 > CH_3O$.

Pyruvate utilization and substituted phenethylamines

The same compounds had strikingly different effects on the "pyruvate utilization" system as shown in table 4. First, the *number* of substituents on the ring was a more significant factor in determining enzyme effect: in general, increasing the number of substitutions caused increased inhibition. And second, as can be seen from an examination of the 3,4,5-substituted compounds, the *nature* of the substituent

had a great influence. Replacing a hydroxy by a methoxy group increased inhibitory action, with still further inhibition brought about by ethoxy substitution. In the penta-substituted compounds, substitution of methyl groups for methoxy groups greatly increased inhibition.

The 2,4,6-substituted compounds were strong inhibitors of this enzyme system, as well as the AP system.

Mescaline analogs and enzyme activity

Table 5 shows the action of a series of side chain, N-substituted and ring analogs of mescaline on AP activity and pyruvate utilization. Certain generalizations can be made about the effect of such variations in structure on enzyme activity.

Increasing the *length of the side chain* as seen by examining compounds 1, 2, and 3; 14 and 15; 20 and 21; 26 and 27; 32 and 33 caused a lessening of inhibition of AP activity, but increased the inhibition of pyruvate utilization. *Saturation of the benzene ring* (seen by comparing compounds 5 and 6; 12 and 13; 18 and 19) had no significant effect on AP activity but did cause increased inhibition of the pyruvate system. *N-methyl substitution* (comparison of compounds 2 and 4; 3 and 5; 20 and 23; 26, 28 and 29) decreased the inhibitory effects of the amines on both enzyme systems, although in some cases only slightly. *N-benzyl substitution* in one case (comparing compounds 15 and 17) markedly decreased inhibition of AP activity, whereas no effect was observed in another case where the primary amine was not an inhibitor (comparing compounds 21 and 22). However, both these N-benzylated compounds strikingly increased the inhibition of the pyruvate system.

Several *amides* can be compared to their corresponding primary amines (compounds 1 and 10; 2 and 11; 20 and 25; 34 and 36). In the AP study, the amides were consistently less inhibitory than their corresponding amines, whereas the effects on the pyruvate system varied. In general the *carboxyl* derivatives were without effect on phosphatase but some depressed pyruvate utilization.

Other neuropharmacological agents and enzyme activity

A selection of psychotomimetic drugs, certain of their analogs, and several tranquilizers were studied for their effects on enzyme activity with results summarized in tables 6 and 7.

TABLE 6.—EFFECT OF PSYCHOTOMIMETIC COMPOUNDS, TRANQUILIZERS AND CERTAIN ANALOGS ON PREPARATIONS OF BRAIN ALKALINE PHOSPHATASE

Compounds (10 mM)	Enzyme Activity	
	Water homogenate	Purified preparation
	(control = 100)	
Mescaline	95	95
3,4,5-trimethoxyphenylisopropylamine	96	104
3,4-dimethoxyphenethylamine	84	89
Dexedrine	100	—
d-LSD-25	138	105
l-LSD-25	136	107
d-LAE-32	121	—
Serotonin	104	70
Bufotenin	154	112
Equanil	119	100
Reserpine	132	108
Chlorpromazine	130	103
Frenquel	140	110
Meratran	—	101

Reaction mixture as described in table 1, using glycine (.05 M) as buffer.

Two types of enzyme preparation were used in the AP study (table 6): one, a supernatant from a water homogenate of brain which had been allowed to settle for 3 hours in the cold; the other, a purified preparation of the enzyme referred to previously.

Using the first preparation of AP, mescaline and two of its analogs were mildly inhibitory. The lysergic acid derivatives, bufotenin, and the tranquilizers all showed activation of the enzyme with bufotenin exerting the strongest effect. Comparing these results with those obtained using the purified preparation of AP, it can be seen that the relative effect of these compounds was essentially the same, although the absolute values changed. Using the purified preparation, activation effects were reduced, and there was an increased inhibition due to serotonin.

A different pattern of effects appeared in the dehydrogenase studies (table 7). Mescaline and its analogs were slight stimulators of LDH. d-LSD-25 had no effect on this enzyme

TABLE 7.—EFFECT OF PYSCHOTOMIMETIC COMPOUNDS, TRANQUILIZERS AND CERTAIN ANALOGS ON LACTIC AND MALIC DEHYDROGENASE ACTIVITY

Compound	Lactic* Dehydrogenase		Malic† Dehydrogenase	
	Conc. of compound	Enzyme activity	Conc. of compound	Enzyme activity
	mM	control = 100	mM	control = 100
Mescaline	10	105	10	89
3,4,5-trimethoxyphenylisopropylamine	10	104	10	85
3,4-dimethoxyphenethylamine	10	104	10	97
Dexedrine	10	110	10	95
d-LSD-25	0.1	99	0.1	103
l-LSD-25	0.1	85	0.1	108
d-LAE-32	0.1	104	0.1	112
Serotonin	5	100	1	94
Bufotenin	5	81	1	94
Equanil	0.1	102	0.1	103
Reserpine	0.1	90	0.1	102
Chlorpromazine	0.1	102	0.1	93
Frenquel	0.1	98	0.1	99
Meratran	0.1	107	—	—

* Reaction mixture: sodium lactate (0.2 M); glycine (0.1 M); DPN (1 mM); pH 9.2; 12.5 c.mm. of 0.5% brain homogenate; 1.0 ml. volume; 25°C.

† Reaction mixture: potassium malate (0.2 M); glycine (0.1 M); DPN (2 mM); pH 10.2; 12.0 c.mm. of 0.25% brain homogenate; 1.0 ml. volume; 25°C.

while its psychotomimetically inactive l-isomer (11) caused inhibition. The serotonin-bufotenin relationship was the reverse of that seen with AP; bufotenin was an inhibitor of LDH while serotonin had no effect. Of the tranquilizers, reserpine exerted a slight inhibition while the others had practically no effect.

On the enzyme MDH, mescaline and its analogs had much the same inhibitory effect as on AP, with the most pronounced inhibition being shown by the isopropylamine analog. The lysergic acid derivatives were slight activators; serotonin and bufotenin had essentially no effect; and the tranquilizers, with the possible exception of chlorpromazine, showed no effect or a slight activation.

DISCUSSION

In the interpretation of data of the type presented here it is necessary to mention certain limitations in the method. The variability in activity of AP in tissue homogenates is well known and may be ascribed, at least partly, to the effects of naturally occurring inhibitors (15). It may be that the activation of this enzyme by tranquilizing agents is due to their action in overcoming such inhibitors. Less variability is observed in the dehydrogenase studies, due perhaps to the fact that a more dilute enzyme preparation is employed, materially diminishing the concentration of inhibitors. Specifically, the amounts of brain tissue per ml. of reaction mixture for each of the enzymes measured are as follows: AP, 2.6 mg.; LDH, 0.62 mg.; MDH, 0.29 mg.

It must be emphasized that relatively high concentrations of powerful drugs had to be used in certain instances to obtain significant effects on the enzymes studied. Such concentrations cannot be related to the *in vivo* state, however, since nothing is known about the concentration of a drug at enzyme sites in an intact cell.

Of the results reported in table 6, the activation effects of the tranquilizers as a group, and of bufotenin, are regarded as especially significant. Such activations are measurable in the presence of magnesium and AMP, both of which increase the activity of the enzyme. It has also been reported that AP activity is increased by phosphorylated vitamin D_2 (18), a finding which could not be confirmed with ester synthesized here.

The LDH enzyme system is relatively resistant to any of the compounds tested, suggesting that anaerobic cycles may be of little significance for this research. In contrast, the pyruvate utilization system was quite sensitive to the influence of the compounds tested, bearing out the findings of Quastel and Wheatley (14) and Schueler (16). It seems more likely that the psychotomimetic drugs exert their influence on aerobic systems and on phosphate metabolism.

The differential effects of the phenethylamines and their analogs on alkaline phosphatase and pyruvate utilization support the idea that an antagonist to mescaline might be found through enzyme studies of this type.

SUMMARY

In a study of mescaline and chemically related compounds, a series of nineteen phen-

ethylamines and thirty closely related analogs were found to exert strikingly differential effects on alkaline phosphatase activity and on pyruvate utilization in brain tissue preparations. In addition, ten other compounds of neuropharmacological interest were tested for their influence on alkaline phosphatase and on lactic and malic dehydrogenase. Bufotenin and the tranquilizers significantly increased phosphatase activity. The lactic and malic dehydrogenase systems were relatively resistant to the compounds tested.

The influence of the mescaline analogs on enzyme activity has been analyzed in terms of the structural configurations of these compounds.

The authors wish to acknowledge the generous supply of compounds provided as follows: bufotenin and serotonin creatinine sulfate from Dr. M. E. Speeter, The Upjohn Co.; d- and l-LSD-25 and LAE-32 from Dr. Kenneth Ericson, Sandoz Pharmaceuticals; 3,4-diethoxy-5-methoxyphenethylamine, 2,4,5-trimethyl-3,6-dimethoxyphenethylamine and 3-methoxyphenethylamine from Dr. P. Hey, Dept. of Pharmacology, University of Leeds, England; N-methyl-3,4,5-trimethoxyphenethylamine from Dr. L. A. Woods, Dept. of Pharmacology, University of Michigan Medical School; Dexedrine, Benzedrex, 4-methoxyphenylisopropylamine, 3-amino-1-(4-methoxyphenyl)butane, N-benzyl-4-methoxyphenylisopropylamine, 3,4-dimethoxyphenylisopropylamine, N-benzyl-3,4-dimethoxylphenylisopropylamine and chlorpromazine from Dr. Alfred R. Maass, Smith, Kline and French Laboratories; Wyamine and Equanil from Dr. W. F. Bruce, Wyeth Institute for Medical Research; reserpine from Dr. A. J. Plummer, Ciba Pharmaceutical Products; Frenquel and Meratran from Dr. Barbara Brown, The Wm. S. Merrill Company.

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PSYCHOPHYSIOLOGICAL STUDIES ON SCHIZOPHRENIC PATIENTS

The Effects of Cortisone Administration and Withdrawal upon Behavior, Serum 17-Hydroxycorticosteroids, Critical Flicker Frequency and Electroencephalographic Tracings[1]

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Introduction

A satisfactory explanation of the mental disturbances which may be associated with ACTH and cortisone administration has not yet been achieved although many studies bearing directly or indirectly upon this problem have been reported. A review of the literature in this field has been carried out by Quarton *et al.* (13). Cortisone psychoses are of much theoretical interest because of their close resemblance to schizo-affective psychosis of spontaneous origin. The fact that they persist for weeks or even months after cortisone has been stopped and are precipitated by steroids comparable to those secreted by the adrenal cortex sets these psychoses apart from the usual drug-induced mental disorders.

A reasonable, but very general, hypothesis is that such mental distrubances are the result of a specific alteration in function of the brain. Unfortunately, there are very few means for studying the activity of the nervous system in intact human subjects. The methods used in the studies consisted of clinical observations on mental status and behavior, critical flicker frequency, and electroencephalograms with cortical analyzer.

Work in this field has also been handicapped by the inadequacy of methods for measuring adrenocortical activity or metabolic processes which might be co-variant with the nervous system disturbance. This situation has been improved by the development of techniques for quantitative determination of plasma 17-hydroxycorticosteroids (8, 9, 12). Using such methods, Bliss *et al.* (1, 2, 3, 4) found that the basal levels of plasma 17-hydroxycorticosteroids and the adrenocortical response to stress and ACTH administration were essentially the same in normal subjects and schizophrenic patients.

Reported studies on the physiological aspects of cortisone psychosis have been limited to the usual indirect measurements of the effects of cortisone on adrenocortical function and tissue metabolism (6, 7). These methods have failed to reveal abnormalities which correlate consistently with the occurrence of mental disorders during cortisone treatment. Metabolic studies of cortisone psychosis have also been hindered by our inability to predict the development of this complication and the relative infrequency with which it appears in patients on steroid therapy. The mental effects of cortisone are about as unpredictable in schizophrenics as they are in mentally normal patients (11).

The work to be reported in this paper started out as a simple pilot study of the effects cortisone administration might have upon critical flicker frequency (CFF). Significant changes in CFF did not occur while the patients were on cortisone, but it was found, unexpectedly, that a decrement in CFF occurred during cortisone withdrawal. It was felt that this might reflect adrenal suppression secondary to cortisone. Accordingly, an experiment was designed to see if this phenomenon could be reproduced and if cross-correlations existed between CFF, EEG, and serum steroid levels. An unexpected investigative opportunity occurred in the course of this study when one of the patients developed a serious aggravation of his mental illness while on cortisone. The mental disturbance was paralleled by anomalous serum steroid findings which will be subsequently discussed.

Summary of Studies

Initial pilot study

1. *Hypothesis.* Significant changes in CFF might occur in subjects treated with cortisone.

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2. *Method.* After a 10-day baseline period, 4 cooperative schizophrenic patients, aged 37–42, without physical disease, were given 50 mg. cortisone q.i.d. for 10 days. The cortisone was then withdrawn at the rate of 50 mg. per day for 2 days and then at 25 mg. per day until total withdrawal had been achieved. Repeated determinations of CFF were carried out during the study.

3. *Results.* (a) No major changes in the mental state of the subjects were observed during the experimental period. (b) No significant changes in CFF occurred during the administration of 200 mg. of cortisone per day.

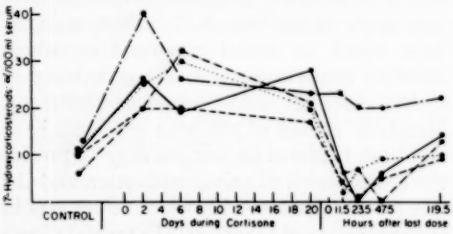

FIG. 1. Serum levels of 17-hydroxycorticosteroids before, during, and after oral administration of cortisone. Subject 1 ———, Subject 2–·–·–, Subject 3– – –, Subject 4 · · ·, Subject 5— — — — —.

Subjects 1–4 were given 200 mg. cortisone per day in divided doses for 20 days; the last dose of 50 mg. was given at 4:00 p.m. on the 20th day. Subject 5 received 200 mg. cortisone per day for 11 days, no treatment on days 12–14, and 150, 150, 120, 100, 75, 100 mg. per day consecutively for the remainder of the study.

CFF was determined during the control period; on the 5th, 13th, and 18th days on cortisone; and 6, 12, 36, and 48 hours after withdrawal. EEG's were carried out during the control period; on the 18th day of cortisone; and in the period 24–36 hours after withdrawal.

(c) CFF determinations carried out on the seventh day of withdrawal, after the subjects had received a single dose of 25 mg., showed a consistently downward trend of 1.5–2.0 cycles per sec. in all cases. These changes were significant at the 0.01 level in 3 subjects and at the 0.05 level in the fourth. These suggestive, incidental findings were the stimulus for a second more systematic study.

Second experiment

1. *Hypotheses.* (a) A decrease in CFF occurs following cortisone withdrawal, (b) that CFF impairment might be paralleled by changes in the EEG, (c) that these neurophysiological phenomena may be related to a period of adrenal hypofunction following abrupt cortisone withdrawal, (d) that such adrenal suppression would be evidenced by serial determinations of blood levels of 17-hydroxy corticosteroids.

2. *Methods.* (a) After a baseline period of 20 days, 5 cooperative schizophrenic patients, aged 23–38, were given 50 mg. cortisone at precisely 8:00 a.m., 12:00 noon, 4:00 p.m., and 8:00 p.m. each day for 20 days. The last dose was given at 4:00 p.m. of the 20th day. With the exception of one sample drawn at 3:30 a.m., 11½ hours after the last dose, blood for the determination of 17-hydroxycorticosteroids was drawn at 3:30 p.m. each day. Constant times of cortisone administration and of blood drawing were maintained in an effort to control variability which could be introduced either by the rate of elimination of exogenous steroids or diurnal variations in adrenocortical function (11). (b) CFF and EEG (with cortical analyzer) studies were carried out throughout the experiment at times noted in the legend of figure 1. They were done at approximately the same time of day on each occasion. (c) Dietary sodium was restricted to approximately 800 mg. per day during cortisone administration. A normal diet was given during the withdrawal period. Serum sodium, chloride, potassium, and fasting blood sugar levels were obtained at intervals throughout the study as a routine precaution.

3. *Results.* The experimental design and the findings on 5 subjects are shown in figure 1. CFF and EEG studies were completed in 4 subjects. As in the pilot study, significant changes did not occur in CFF during cortisone administration; however, in contrast to the previous study, decrements in CFF significant at the 0.05 level occurred during cortisone withdrawal in only 2 of 4 subjects. EEG's, analyzed for average frequency, dominant frequency, alpha incidence, alpha amplitude, and response to photic driving, showed no significant changes throughout the study. This includes the period 24 hours after withdrawal of cortisone when serum steroids had fallen to very low levels. Serum sodium, chloride, potassium, and fasting blood sugars when determined during the experiment were found to be within normal limits.

Serious deterioration of the mental state and

behavior of subject 5 precluded completion of the CFF and EEG studies. Concern about his mental state led the investigators to reduce his cortisone dosage prior to the 20th day. These dosage changes are described in the legend of figure 1. On the 14th day of cortisone, subject 5, who had previously been communicative, cooperative, and quiet, showed a peculiar hesitancy of speech, was very withdrawn, appeared frightened, and was almost mute. He admitted no physical distress other than some feeling of discomfort in the frontal portion of his head. The following day he was completely mute and immobile except for chewing movements of his jaw and periodic shaking of his arms. He would not eat. *Cerea flexibilitas* was present. Slight improvement appeared 3 days after cessation of cortisone treatment. Two weeks later, however, he was still mute, very withdrawn, and underactive, but did eat with encouragement. He returned to his usual behavior about 6 weeks after stopping cortisone. There was no past history of catatonic stupor or episodes similar to that observed on this occasion. Serum sodium, potassium, and chloride levels were within normal limits when determined on the first three days of this relapse and at weekly intervals thereafter. Significant changes in mental state did not occur in the other four subjects.

It was of considerable interest to find that the serum steroid values in subject 5, as shown in figure 1, did not follow the pattern of the other subjects. The most surprising difference was the failure of his steroid levels to fall during the withdrawal period. His level on the second day was higher than those of the other subjects, but it is doubtful if any significance can be attached to this single determination. During the remainder of the cortisone period, his levels were in a range comparable to the others. However, it should be noted that his dose preceding the 3:30 p.m. blood samples on the 17th and 20th days had been 25 rather than 50 mg.

Further studies on subject no. 5

In view of the unusual serum steroid pattern of this subject, it was decided to carry out further studies of his adrenal function when he had returned to his usual mental state. A standard ACTH test was done (10). Two weeks later a compound F tolerance test was carried out (5). The results obtained fall within the normal range (cf. table 1).

TABLE 1

		Serum 17-OH Steroids, Micrograms /100 Ml.
ACTH Test	Control	13.9
	1st hour during infusion of ACTH	30.0
	2nd hour during infusion of ACTH	36.0
	4th hour during infusion of ACTH	39.0
Compound F Test	Control	18.4
	30 minutes after cpd. F	100.0
	1 hour after cpd. F	69.0
	2 hours after cpd. F	50.0
	4 hours after cpd. F	27.0
	6 hours after cpd. F	14.0

Serum levels of 17-hydroxycorticosteroids in subject 5 during a 6-hour intravenous ACTH infusion and following the intravenous administration of compound F.

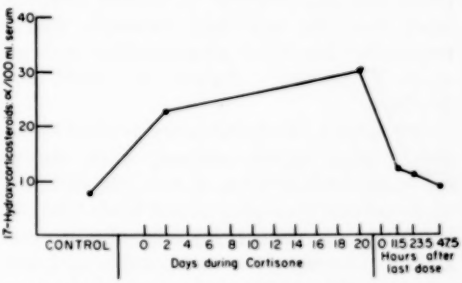

FIG. 2. Serum levels of 17-hydroxycorticosteroids in subject 5 before, during, and after oral administration of 200 mg. cortisone daily for 20 days.

Two weeks after the compound F tolerance test, subject 5 was again given 200 mg. of cortisone daily for 20 days (figure 2). The primary interest was in his steroid response to abrupt cortisone deprivation. The results of this second cortisone experiment (cf. figure 2) were again of interest. While his steroid levels did fall more after cortisone withdrawal than in the previous study, they did not run below his control levels.

Discussion and summary

It has been demonstrated by serial determinations of 17-hydroxycorticosteroids that in 4 out of 5 subjects treated for 20 days with

cortisone a marked decrease in serum levels occurred following abrupt withdrawal of the drug. This was evident in samples drawn 11.5, 23.5, and 47.5 hours following the last dose of cortisone.

CFF did not change significantly during cortisone administration. There was, however, a consistent downward trend in CFF in the 4 cases studied during the period 12–48 hours after cortisone withdrawal. This decrement was significant at the .05 level in two cases. Electroencephalograms showed no change in the subjects studied during either cortisone administration or 48 hours after abrupt withdrawal. The findings suggest that serum 17-hydroxycorticosteroid levels under the experimental conditions described can fluctuate within a wide range without being associated with significant EEG changes. It should be emphasized, however, that the cortisone-induced hypoadrenalism lasted only 12 to 48 hours and was probably so rapidly compensated that the secondary metabolic effects responsible for EEG abnormalities such as occur in Addison's disease (14) could not develop.

One subject (no. 5) has been described whose mental state became seriously worse during cortisone administration. It was coincidentally observed that his serum steroid levels failed to fall during the 48 hours following abrupt cortisone withdrawal. It is not possible to know whether this relapse in mental status was etiologically related to the effects of cortisone and might therefore be regarded as comparable to "cortisone psychosis", or whether it was occasioned by some coincidental, undetected psychodynamic circumstances during the study.

In either event, the anomalous response of this subject to cortisone administration is of interest, but at the present time only speculative explanations can be offered. One is that a severe mental disturbance, cortisone-induced or spontaneous, may constitute sufficient "stress" to preclude the depression in adrenocortical function which is normally induced by adrenal steroid administration. This in turn suggests the presence of an emergency mechanism, presumably involving the hypothalamic-pituitary-adrenal system, which can supersede the usual compensatory process by which adrenal suppression occurs in response to exogenous steroids. Another hypothesis is that the anomalous steroid response seen in this subject indicates either an abnormality in a pituitary-adrenal or adrenal system concerned with regulation of adrenal output or an acute change in metabolism of steroids with a 17,21-dihydroxy-20 keto sidechain. Such abnormalities could be etiologically related to the occurrence of a cortisone psychosis.

Grateful acknowledgment is given to Dr. Kenneth Kooi, Assistant Professor of Psychiatry (Neurology), University of Utah, for the electroencephalographic studies reported in this paper; to Mr. Reed Boswell, Clinical Psychology Trainee, University of Utah, for carrying out the many CFF determinations; and particularly to Dr. Leo T. Samuels, Chairman and Head, Department of Biochemistry, University of Utah, for his advice and encouragement to this inter-disciplinary project.

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ARE THE FIRST BORN MORE SUSCEPTIBLE TO FUNCTIONAL MENTAL DISEASES?

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Recently many studies have been made to determine whether the order of birth[2] of a child among his brothers and sisters can have any effective influence on his future mental growth and development, or his future susceptibility to mental aberration or anomalies. As early as 1874 Galton (8), in his studies of English men of science, their nature and nurture, was supposed to have shown that the first born is specially gifted. Similar studies in the field of birth order and intelligence, birth order and delinquency, birth order and language development, birth order and emotionality were also made with objective references by Gini (10), Havelock (13), Jones (16), Goring (12), Dugadale (7), Stern and Stern (23), Goodenough (11), and others.

The studies of Brousseau and Brainerd (3) and Vander Scheer (27) on mongolism or the earlier studies of Mitchell (18), Down (6) (1887), and others are more or less subjective. They depended for their conclusions on simple observational findings or clinical data. In recent times, objective studies of birth order in its relation to mental attainments and mental defects were made, depending on I.Q., C.I. and other statistical procedures. Of these, the most important pioneering works were done by Dayton (5), Arthur (2), Pearson (19), Terman (25), Thurstone (26), Cattel (4), and Hsiao (14). Unfortunately the findings of these researches are not decisive. Some placed the first born to a superior position, others the last born, and there were many who got zero correlation between the birth order and mental development.

From the above studies, naturally our interest was drawn to a similar investigation to determine whether there is any relation between the birth order and mentally maladjusted personalities as observed in two of our mental clinics at the Lumbini Park and R. G. Kar Medical College. For this purpose, we made a study of about two thousand cases. Of this total number of cases, the full heredity and birth order could be traced only in fifteen hundred cases; in other cases due to circumstances beyond our control, the full heredity history and the birth order of the patients could not be traced.

This number of mentally maladjusted persons, when arranged according to their birth order, stands as in table 1. From this table, the incidence of functional mental diseases seems to follow a descending order in relation to the birth order, i.e., the more we go down in the scale of birth order, the lesser the number and percentages of siblings appear to be susceptible to the functional mental maladjustments; but it is only a table of raw data and thus can never form a sure guide for our purpose. To obviate any possible error in our forming a true notion, side by side with table 1 of observed data, we have taken an ideal comparative table, based on statistical probability expectation. This ideal expectation table depends on the simple knowledge that in diseased families of one sib size, the first born are naturally all diseased, so in one sib size families 100 per cent are first borns and all are equally susceptible. In families of two sib size, 50 per cent of each of the siblings, i.e., first or second borns, are equally susceptible. Similarly in 3 sib size families each sibling is 33.3 per cent susceptible, in 4 sib size 25 per cent, in 5 sib size 20 per cent, and so on.

Thus table 2 (with the calculated statistically expected number of cases) for each sib size family stands as shown.

If a comparison is made of the percentages of actually diseased with the statistically calculated expected cases, we find that only in the birth orders, namely of the first, third and tenth, does the actual exceed the statistically expected number. Thus apparently the

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[2] We have assigned here birth number on the basis of all children born, including the still births; of course, we have to leave out the abortions, miscarriages, etc., as the reliable data on them are not obtainable.

first, the third and the tenth borns seem to be more susceptible to functional mental diseases as observed in our series of cases (table 3). But we know that the expected percentages have a standard range of variation or normal limit of variation which can be calculated by the formula

$$\sqrt{\frac{PQ}{N}} = \sigma_D = \text{Normal range of variation as expressed in percentage (9)}$$

$$\frac{P(1-P)}{N}$$

Where $Q = 1 - P$.

where P = percentage of time the given birth order occurs; Q = 1 − P; N = number of total cases.

We have percentage of particular data $\pm\sigma_D$ = the normal limits of variation of the statistically determined susceptibility of specific birth order to functional mental diseases. We have $\sigma_{D_1} = 1.1$; $\sigma_{D_2} = 0.9$; $\sigma_{D_{10}} = 0.8$:

SoF_{nvl} = First borns' normal variation limit as calculated by the above formula is $26 \pm 1.1 = 24.9$ to 27.1 ..... 1)

Th_{nvl} = Third borns' normal variation limit as calculated by the above formula is $16.4 \pm 0.9 = 15.5$ to 17.3 ..... 2)

Te_{nvl} = Tenth borns' normal variation limit as calculated by the above formula is $0.9 \pm 0.8 = 0.1$ to 1.7 ..... 3)

From the above, we find that excepting in the case of the first borns, the normal variation limits of the third and the tenth borns cover the actual excessive cases that we have observed at those two levels. So they (the third borns and the tenth borns) do not significantly surpass the normal variation limits. Thus by statistical calculations, we find that in our series of observed cases only the first borns exceed the normal variation limit; as such the first borns only should be considered to be more susceptible to functional mental diseases in our series of cases. In this connection, it will be interesting to note that similar excess of the first borns was also observed by Goring (12) among English criminals, by Still (24) among certain types of diseases, and by Pearson (19) among the handicapped.

Naturally, we are confronted, at once, with the question—why is the greater selective susceptibility of the first borns? On a superficial analysis, it may appear that this greater susceptibility is more apparent than real and that it is due to a natural surplus of the first borns in the general population, due to the following reasons:

TABLE 1

Birth Order	Total Number of Cases at Each Level of Birth	Percentage of Cases at Each Level of Birth
First born	445	29.6
Second born	293	19.0
Third born	262	17.0
Fourth born	176	11.7
Fifth born	136	9.0
Sixth born	76	5.0
Seventh born	47	3.0
Eighth born	24	1.6
Ninth born	25	1.6
Tenth born	16	1.0
Total	1,500	

TABLE 2

Family of Different Sib Size	Actual Number of Families at Each Sib Level	Statistically Calculated Number of Cases at Each Birth Order
Sib number 1	79	First born 388.7
Sib number 2	127	Second born 309.7
Sib number 3	172	Third born 246.2
Sib number 4	204	Fourth born 188.9
Sib number 5	235	Fifth born 137.9
Sib number 6	177	Sixth born 90.0
Sib number 7	153	Seventh born 61.4
Sib number 8	123	Eighth born 39.4
Sib number 9	96	Ninth born 24.0
Sib number 10	134	Tenth born 13.4
Total families	1,500	

TABLE 3

Birth Order	Observed Number of Cases at Each Level of Birth Order	Statistically Expected Number of Cases at Each Level of Birth Order
*First born	445 (29.6%)	388.7 (26%)
Second born	293 (19.0%)	309.7 (20%)
*Third born	262 (17.0%)	246.2 (16.4%)
Fourth born	176 (11.7%)	188.9 (12.6%)
Fifth born	136 (9.0%)	137.9 (9.2%)
Sixth born	76 (5.0%)	90.0 (6.0%)
Seventh born	47 (3.0%)	61.4 (4.1%)
Eighth born	24 (1.6%)	39.4 (2.6%)
Ninth born	25 (1.6%)	24.0 (1.6%)
*Tenth born	16 (1.0%)	13.4 (0.9%)

BIRTH ORDER →	1	2	3	4	5	6	7	8	9	10
TOTAL NUMBER OF CASES OBSERVED AT EACH BIRTH ORDER →	445 (29·6%)	293 (19·0%)	262 (17·0%)	176 (11·7%)	136 (9·0%)	76 (5·0%)	47 (3·0%)	24 (1·6%)	25 (1·6%)	16 (1·0%)
TOTAL NUMBER OF CASES EXPECTED AT EACH BIRTH ORDER →	388·7 (26·0%)	309·7 (20·0%)	246·2 (16·4%)	188·9 (12·6%)	137·9 (9·2%)	90 (6·0%)	61·4 (4·1%)	39·4 (2·6%)	24 (1·6%)	13·4 (0·9%)

FIG. 1

1) Birth control among the population limits the later borns. But as the maximum number of our recorded cases were born 20 to 30 years before, this factor cannot be considered of much importance since at that period birth control was not practiced at all in India. Also birth control is practiced in India even now only by a selected few; therefore it could not be of much importance in our study.

2) We know that whenever the general birth rate of a place is diminishing, the percentage of the firsts in any age level will appear higher. But as the census reports in India show that the birth rates for the two censuses (1931 and 1941) which concern our data were in the increase (the rate for 1931 was +10.6 per cent; for 1941 was +15 per cent), the question of diminishing birth rate and its influence cannot arise.

3) In many cases it is quite possible that we have not been able to eliminate the effects of incomplete families. It is obvious that later borns are more numerous only in complete families. It is not possible for us to foresee how many more children will be added to the family afterwards. This has naturally given a spurious weightage to the earlier borns. In answer to this, one can only add that to counteract this effect there is the natural factor of a much higher death rate, at a very early age, among the first borns; therefore many of the first borns who may have added to our existing case numbers died before they showed any manifestation of the disease.

4) Lastly, in the incomplete families, as well as in all other families, it may be pointed out that we have longer periods and greater opportunity of observing the defects that are developing in the first borns. But the fact stands out that in our case records the first borns are in no way significantly older in age than other observed cases.

Thus we find that the greater susceptibility of the first borns is not spurious but real. In the following pages there is a discussion to see whether there is any possible reason for this greater susceptibility of the first born. This analytical study has been made under the following heads:

a. Heredity influence

b. Environmental influences → Psychological / Physical

Heredity Influence

Heredity is really a limitation put on a person by nature, beyond which he or she cannot go. Unfortunately in connection with any study of mental inheritance, there arise some inherent difficulties because so far as the physical personality is concerned, we can easily dissect it out into several independent units or clear-cut characterestics, e.g., hair color, facial contour, stature, eye color, etc. So far as the mind is concerned, it becomes pretty difficult to analyze out its constituent units. For example, even with our intensive studies and works on intelligence, we do not know whether intelligence itself is a unitary substance, or if it is a complex of few units. As a matter of fact, all that we can know about the mind is learned only through its functions, that is, the mind can be studied only from the functional standpoint. Its physical as well as physiological correlates are either unknown or only known vaguely or partially. Unfortunately all that we know about inheritance is in relation to the structure. Though the function is only an expression of structure, yet the same structure can give rise to quite different types of function; so unless and until we find definite physical correlates of mental functions, there remains a primary and fundamental difficulty in the study of mental inheritance.

In spite of this difficulty, there has been extensive work done in the field of mental inheritance since Mendel. The physical basis of mental and physical character traits of the progeny is found to lie dormant in the parental gonadic chromosomes and their genes. All that we know about these chromosomes and genes, that are relevant to this paper, are as follows:

1) The gene-beaded chromosomes are supposed to be the bearers of the character traits for the future generation. These are not only the magic-script which are just going to be revealed in the life of the offspring, but they are also the executive which will help

in the manifestations of all these potential and latent characters that may lie dormant in the progeny.

Biologists have shown that at a very early period of fetal development, the germinal cells are separated out and remain completely isolated from the main mass of somatic or body cells. The germ cells remain almost rigidly constant in their character, uninfluenced by any of the subsequent changes that may take place in the surrounding somatic cells.

Doubt has recently been thrown on the theory of structural constancy of gene-beaded chromosomes by Schrödinger (21), the famous physicist-philosopher. In his pamphlet "What is life", Schrödinger quite rationally observes that real physical structural constancy is not possible in the physical world; its nearest approximation is possible only in statistical or probability constancy of structure. However, statistical constancy which presupposes the congregation of a large number of atoms is not possible where we are dealing with the incredibly small group of atoms, as in the genes. How then do the genes play such a constant and dominating role in the very orderly and lawful events of biological transmission of parental characters? The question was raised by Schrödinger, and the answer was also suggested by him. He says that from the facts of biological laws of hereditary transmission, we shall assume that the structure of a gene is to be, for all practical purposes, that of a large molecule. This molecule, further, is regarded to be a solid and an aperiodic crystal. By this assumption the difficult problem of how the genes maintain a constant physical structure is solved.

First, it is true that vast numbers of different arrangements of the atoms in the genes are possible. Since the energy requirement for any of these changes is too high, any such change of arrangement of atoms in the genes is a rare event and occurs only when a spontaneous or induced mutation takes place. Thus for all practical purposes, the constancy of the gene structure can be assumed, and rigid and orderly transmission of parental characters is possible.

Secondly, all that we know about the chromosomes and genes are as follows: In human beings 24 chromosomes come from each of the parents to give rise to 24 pairs = 48 chromosomes of the future offspring. Various types of permutations and combinations of the parental chromosomes are possible and do occur in the formation of the zygot. What really regulates the different types of combination of these contributing factors is not yet known. There is no known order of combination of parental chromosomes or genes; possibly the combination totally depends on chance. Thus it is not predictable beforehand what specific parental character traits are going to be manifested in a child of any particular birth order. There is no known relation between the order of pregnancy and the combinational pattern either of the chromosomes or the genes, nor is it experimentally possible to determine the specific nature of the combinational results, if there be any, of the various series of 1st, 2nd, 3rd, etc. of the ejaculated sperm cells of the father uniting with any of the 1st, 2nd, 3rd, etc. of the mother's ovum. A general predictability of various combinations of parental characters is possible, depending on the laws of probability, but that does not assign any specific inheritance to any particular order of birth. All that we know about the regulations of combinations are as follows: a) The character traits of the offspring are a mosaic pattern of the parental character traits; and in the formation of this mosaic pattern 1) there can never be a blending of the unit character trait of the parents; 2) half of the character traits are contributed by the mother and the other half by the father, each parent contributing 50 per cent of the offspring's character traits. This really is only a deduction from the law of ancestral inheritance of Galton. The law states that the two parents contribute themselves on the average of one-half of each inherited faculty; the four grandparents contribute between them one-quarter or each of them; one-sixteenth; and so on: The sum of the series $\frac{1}{2} + \frac{1}{4} + \frac{1}{8} + \frac{1}{16} + \ldots$ to infinity being equal to one, as it should be. Further it is the property of this infinite series that each of the terms is equal to the sum of all other terms that follow, e.g., $\frac{1}{2} =$

$\frac{1}{4} + \frac{1}{8} + \frac{1}{16} + \ldots$. The average contribution of each ancestor is thus stated definitely, the amount of contribution diminishing with the remoteness of ancestors.

b) The law of filial regression may be called the tendency to mediocrity. Galton (8) found on statistical study that on the average extreme peculiarities of parents were less extreme in children.

c) Some characteristics were found to be linked up with specific character traits, e.g., variability probably is linked up with male sex character.

d) There is no known relation between the age of the parents and the inheritance of parental characters by the children.

e) Experience or acquired qualities or defects of parents are not inherited by the next generations. Therefore good or bad qualities or habits that may be acquired with advancing age can never influence the mental equipment of the future generations by inheritance. Recently this has been challenged by the Russian Michuristic school as represented by Lysenko (17) and his followers. They claimed that experimental transmission of acquired characters was possible, but even according to Lysenko this was a very complex process, and very complicated changes in the body were essential prior to the possible transmission of an acquired character of the parent in the child. He postulated that transmission of an acquired character can take place only in three stages—in the first stage there is the shattering or shaking of heredity. By this process of shattering there is breaking down of the stability which is normal to the heredity constitution. Once the shattering process is effected, the heredity is supposed to become more labile and plastic.

So far as our cases are concerned, we know that even if we accept Lysenko's view, the question of a new character emerging out in the progeny still requires a few generations' concentrated activity, and if such a change comes into existence in any generation, the whole generation will be influenced by this character change. There cannot be any special or specific selective superiority or inferiority in relation to a particular birth order. Many of the experimental findings obtained by the Michuristic school were not universally accepted. These findings were not corroborated by other scientists (15) working outside Russia. Critics of Lysenko stated that he had neither taken scientific precautions in his experiments, nor had he done any control experiment or statistical check-up of his findings. The experimental findings seemed biased and might well have formed a preconceived idea just to fit in and confirm scientifically the political philosophy of Soviet Russia that all human beings are born with equal potentiality and possibility.

Thus we find that up to the present time there is no positive proof that acquired character may be transmitted into the next generation, hence there cannot be any selective influence of heredity on a particular or specific birth order.

Environmental Influences

Let us next attempt an analysis of the environmental factors to see whether they may in any way influence selectively any particular birth order. The environment can be divided broadly into two groups—physical and socio-familial.

Physical

Scientifically speaking the environment begins exerting influence from the start of inception. The uterus itself is an important environmental envelope. Experiments have proved that the fetus in its intrauterine life is influenced by a) exogénous as well as by b) endogenous poisons to which the mother's body may be exposed. Such metabolic diseases, as myxedema, diabetes mellitus, in the mother may cause cretinism and abortion of fetus. Syphilis or heavy metal poisoning, such as of lead, arsenic, etc., will inhibit the proper growth of the nervous system of the offspring; alcohol and other habitual use of narcotics may make the nervous system of the future child vulnerable to malformation or disease. In some way or other the nervous system represents the physical side of the mind.

We must never lose sight of one fact: that all these exogenous and endogenous poisons may influence any of the offspring, independent or irrespective of the birth order.

Some biologists believe that with the advancing years of the mother the endocrine

function begins to wane, and that as a result the children born at this late age of the mother are generally immature in body and mind. In this study, the idea that mongolian idiocy is caused by a supposed low level of maternal endocrine function should receive necessary attention. Though some biologists believe that as a result of a natural fall in the hormonal level in the elderly women their children are susceptible to mental subnormality, we cannot persuade ourselves to believe that this is correct because a) it lacks authentic proof, b) its corroborative findings by other scientists are not obtainable, c) the fuller knowledge about the working of the endocrine is still not very clear, i.e., how the endocrines maintain their harmonious action and what regulates their secretory equilibrium, etc. It has not been proved that with advancing age, especially during the fertile period, the hormonal concentration in the mother loses so much that the children will suffer. Lastly, even if we accept this to be correct, it does not in any way explain the greater susceptibility of the first borns as observed in our series of cases; especially when we remember that early marriage is the rule rather than exception in India, and the patients are almost all the offsprings of mothers in their teens.

There are, of course, some known important factors which are found to be effective selectively on the first borns. These are as follows: First borns are generally exposed to the maximum amount of difficulties during their birth. Traumas during birth, prolonged labor, instrumentation during delivery are too frequent in cases of the primigravida. Birth shock is also more common in the first borns. Eclampsia and other forms of toxemias of pregnancies are to be observed more during the first pregnancy, and necessarily the first child suffers most. Pre- and post-maturity are also observable more in the first borns. Physiological factors as well as the anatomical changes of the maternal pelvic regions are all favorable for the later borns. All these factors may add to the greater susceptibility of the first born to functional mental diseases due to extra strain and stress during his birth.

Socio-Familial

In the majority of our cases, the first borns are the offsprings of mothers in their teens; thus they are the children of physically and mentally immature parents. As a result of this, the great majority of these parents are quite inexperienced in child psychology or ideal methods of child rearing and child nursing. They may not know, because of their youth and inexperience, anything about the normal and natural development and growth of a child so that slight and early deviations from the norm in the case of the first borns may not be taken care of. Thus a large number of the first borns failed to get the necessary expert advice early. As a result later on more of them come out as full-bloomed diseased personalities.

The latest and improved medical and social aids are also more available for the later borns. Generally the majority of the modern families show economic improvement after the birth of the first or second child, as with advancing age naturally the income of the family increases. As a result of this, the later borns come into the midst of much easier, happier and in more secure familial surroundings. Later borns in many cases are planned children, whereas the first borns are in the majority unplanned children of inexperienced couples. Many advantages and benefits which are denied to the first borns come within easy reach of the later borns. In the present day life of grim struggle, competition, and conflict, the course of the future life can only be smoothed out in favor of the economically superior.

In a poor country like India (where the joint family system is still in vogue), the eldest child is often called upon to share the responsibilities of the family very early. Sometimes the family burden falls on his young shoulders in the very prime of his life, when he himself should be under the care of some one else.

Stanley Hall is of the opinion that to be the only child is a disease in itself, and this is a disease, unfortunately, through which every first born has to pass at least for sometime in his or her life. The only rare exception is the case of a twin.

Adler (1) says that the first child is ap-

proached by the parents with an inordinate solicitude. Constant anxious attention to them by the parents, ignorant of child psychology, makes the first borns believe that the world is a very hostile place. The attempt to hide everything unpleasant from them makes them weaker mentally, and any and every difficult situation of life may upset them. The first borns, receiving all the cares and attentions for some of the early and psychologically significant formative years of their lives, tend to be over-dependent and rather hypersensitive to all the trying situations of life. Their over-dependence on parents and others in their early life may well instill in them a love for life-long parasitism, and this may form the nucleus of their after-life mental abnormality. By taking advantage of the disease, they may well escape from the stern realities and responsibilities of life.

Further, because of their share of maximum family privileges and favors, in their lives they become very conservative and almost always like to keep up the "status quo" position. They react very unfavorably to any reformation, innovation, or any sudden change.

Whenever there are several brothers and sisters in a family, each individual sibling has a different pattern of psychological milieu of his own. This may be a tremendous influence in the molding and formation of the personality characteristic of an individual.

The psychological effect of the position of the child in the total family constellation colors the individual's life more than either his heredity or other environmental factors.

Specific effect or influence (if there be any) of heredity or physical environment in the moulding of the character and personality is not predictable so far as each birth order is concerned; but the psychological influence of the family constellation to a great extent is determinable.

Lastly, the first born stands in a different relation both to his parents as well as to his younger siblings. Speaking from the psychoanalytical standpoint, this early relation will have a tremendous after effect in the shaping of the future pattern of the first born's life. The first borns, when they come, change the whole preexisting family conditions and the love life of the parents. First borns are likely to find much greater difficulties in the normal developments and adlustments of their psycho-sexual life than the jater borns, due to greater possibilities of parental fixations and other difficulties natural in the novel and inexperienced background of the newly-formed child-parent relation. Thus the early life difficulties of the first borns in their total family constellation may well form the nucleus of their future life mental abnormalities.

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THE VISUAL FIELD IN THE SENSORIMOTOR INDUCTION SYNDROME AND ITS CHANGES UNDER THE INFLUENCE OF COLORS[1]

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It is characteristic of the sensorimotor induction syndrome (1, 3, 4, 5, 6, 7, 8) that the unilateral postural deviations induce disturbance of sensory perception. Of these, impairment of visual functions is of chief significance. A primary visual symptom is the displaced perception of spatial coordinates which usually manifests itself in the eye which corresponds with the side of the disequilibrium. Incongruity in the perception of the vertical and horizontal coordinates by each separate eye results, on viewing with both eyes, in the "coordinates' optic vertigo" (2). Secondary symptoms are quantitative and qualitative changes of visual perception appearing in the homolateral eye. The quantitative change appears clinically as a reduced or enlarged perception of an optic stimulus in the sense of micropsia or macropsia. The qualitative dedifferentiation in visual perception manifests itself in the homolateral eye by imperfect discrimination of color shades, complete dissolution of color perception in the extreme, and by fusion of a narrow-spaced dotted line into a continuous one.

Routine examination of the visual field showed no distinct deviation from the normal in most patients. Further observations, however, led to renewed investigation with regard to changes of the field of vision. It was repeatedly observed that patients, when seeing with the eye on the disequilibrated side, were at first able to read a given text, but had to give up after a while as vision became blurred. In the different patients blurred vision appeared after a shorter or longer time, in all cases originating on the temporal side. The disturbed perception of colors mentioned above, appearing at once or after a certain amount of time, also affected chiefly and most distinctly the temporal side of the visual field. These observations, together with a supposed influence of a latency period, brought to mind the assumption of a dynamic change of the visual field. As will be shown below, investigations confirmed indeed this assumption and showed in addition that the resulting changes of the field of vision could be distinctly influenced by colors.

I

Dynamic changes of the visual field

Case 1: Sch. Sch., a woman, aged 26, suffered from repeated attacks of loss of consciousness for the past three years. As a space-occupying process was suspected, air studies were performed several times, all of which were negative. Clinical examination revealed a right-sided systematized impairment of the equilibrium, presenting the features of the sensorimotor induction syndrome.

The single symptoms of this syndrome were described elsewhere. With regard to this study it should be mentioned that the following chief disturbances existed in this patient: 1) motor disturbances resulting in a right-sided postural deviation of the whole body and its ipsilateral extremities. 2) displacement of spatial coordinates and geometrical figures when seen with the right eye; 3) macropsia, impairment of color perception and disturbed discrimination of spatially close optic stimuli, when seen with the right eye; 4) deviation in the tactile and haptic localization of the vertical and horizontal; 5) macrostereognosis and homolateral overestimation of weights on the right side; 6) systematic influence of colors on motor and sensory functions.

This patient presented thus a right-sided disequilibrium with all features of the sensorimotor induction syndrome. The visual field, which was repeatedly examined at different times, was always found to be normal on both sides. However, when at the same session the test was performed consecutively, it became apparent that this method of examination revealed actual changes in the field of vision. The visual field became increasingly constricted affecting the right eye only (fig. 1).

After these findings, the influence of colors on the visual field was tested. Using the same procedure of consecutive examinations in the

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same period of time, a blue glass was put before the right eye of the patient. Under this condition the concentric constriction did not appear at all. Under the influence of red, however, the right visual field became increasingly constricted in a shorter time and to a higher degree. When the red glass was quickly exchanged for a blue one, it became apparent that the markedly constricted right visual field became increasingly dilated during the consecutive tests (fig. 2). When the same test was used for the left visual field, no changes were found with or without colored glasses.

Case 2: G. B., a woman, aged 34, felt unsteadiness when walking for the last two years. At times this impairment increased so much that she was confined to her bed for weeks on end. Sometimes she also suffered from vomiting. When cerebellar symptoms appeared too, a cerebellar tumor was assumed, and the patient was admitted to the neurosurgical department.

On examination no signs of increased brain pressure were found. X-ray of the skull, electroencephalography and ventriculography were normal. Reflexes, sensibility and pyramidal motility showed no deviation. Examination of the eyes also gave normal results in every respect. There existed, however, an impaired equilibrium on the left side which in part showed the features of the sensorimotor induction syndrome. The following single symptoms were found: 1) descent and outward deviation of the left arm and leg with compensatory ascent of the right arm; 2) a tendency to fall to the left and past-walking to the left; 3) deviation to the left in haptic localization and underestimation of the size of objects when touched with the left hand in the sense of microstereognosis; 4) sensitivity of the left eye to colors.

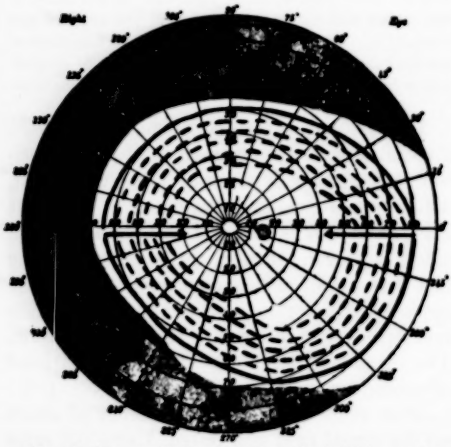

FIG. 1. A normal visual field at the initial examination. Successive constriction of the visual field.

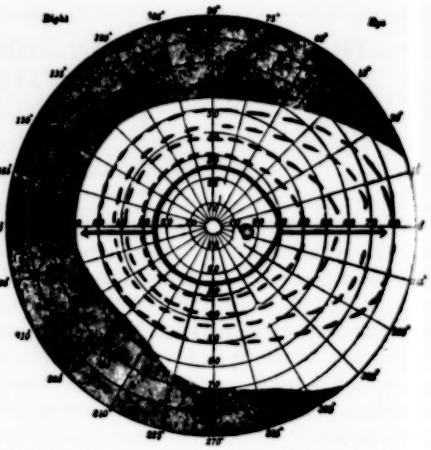

FIG. 2. The constricted visual field under the influence of red. Successive widening of the constricted visual field under the influence of blue.

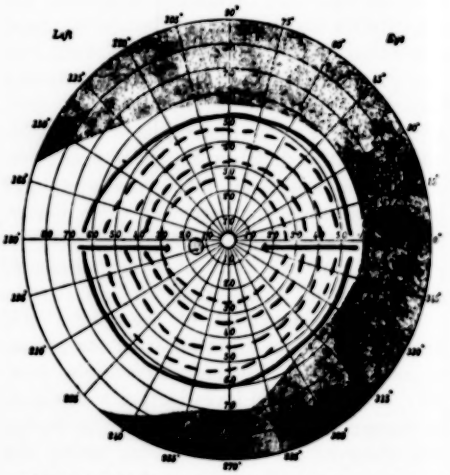

FIG. 3. Initial spontaneous constriction of the visual field. Successive constriction of the visual field.

In this patient the impaired equilibrium, with the features of the sensorimotor induction syndrome, manifested itself on the left side. On first examination the left visual field was found to be constricted, the temporal part being more affected. During consecutive examinations the constriction of the left visual field increased continuously (fig. 3). When a red glass was put before the left eye of the patient, the concentric constriction increased further, occurring with striking speed. The patient,

however, felt so badly that the test could not be wholly concluded. Substituting a blue glass for the red one produced a very distinct and rapid change. On consecutive testing of the left visual field an increasing widening took place until normal limits were attained (fig. 4). The effect of blue was sufficient to correct the existing spontaneous constriction. In the right visual field there existed neither a spontaneous deviation nor an influence exercised by colors.

Case 3: L. A., a woman, aged 42, suffered occasionally from dizziness and unsteadiness when walking during the last three years. Two years ago the patient was admitted to the neurological department. Then a slight weakness of the left arm and leg was found while reflexes were normal. On the same side of the body there existed in addition a diminution of superficial sensibility in all its qualities and a quick expiration of the sense of vibration. This impairment was not constant. On control examinations after general improvement it was hardly detected or not present at all. X-ray of the skull, electroencephalogram and spinal fluid were normal.

When the patient was admitted again, disequilibration which had the typical features of the sensorimotor induction syndrome was found on the left side. Without stressing details the following chief disturbances should be mentioned here: 1) motor disturbances which resulted in a left-sided postural deviation of the whole body and its ipsilateral extremities; 2) left-sided visual displacement of spatial coordinates and geometrical figures and micropsia when seeing with the left eye; 3) microstereognosis and underestimation of distances with the left hand; 4) a mutual sensorimotor influence;

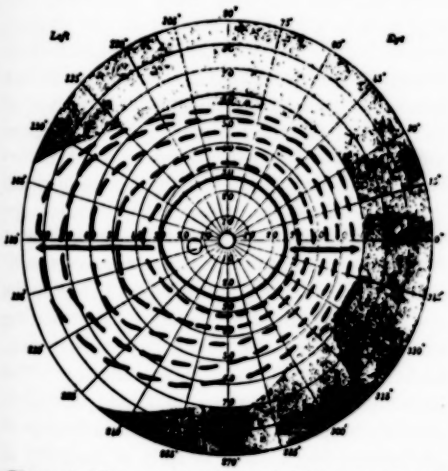

FIG. 4. The constricted visual field under the influence of red. Successive widening of the constricted visual field under the influence of blue.

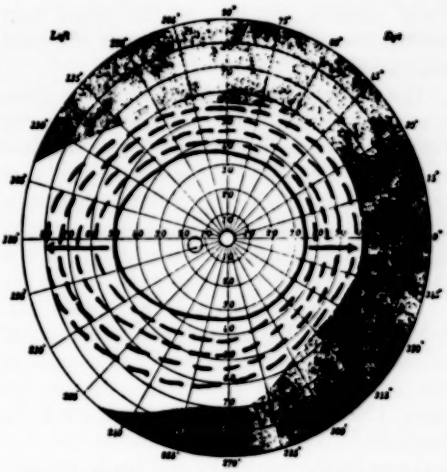

FIG. 5. Initial spontaneous constriction of the visual field. Successive widening of the constricted visual field under the influence of blue.

5) systematic influence of colors on the motor and sensory disturbances.

Already on first examination of this patient a concentric constriction of the left visual field was found to be present, while the right visual field was normal. On successive tests the left visual field became increasingly constricted, while the right one did not change. When a blue glass was put before the patient's left eye and the visual field was tested repeatedly, it dilated more and more until it finally showed normal limits (fig. 5). When a red glass was put before the left eye, a drastic change in the patient's condition occurred. Vision became blurred, the patient suffered from nausea and palpitation and began to cry. Therefore a determination of the visual field could not be performed. The patient stated that the darkening set in from the temporal side.

II

Comment

The three patients described above presented the typical picture of the sensorimotor induction syndrome. As is known, this syndrome is based on the fact that changes of sensory perception can be induced by postural deviation. These induced sensory changes affect haptic, tactile and, as was mentioned above, visual perception in many ways. As was shown in

these patients, changes of the visual field belong to the induced disturbances of visual perception.

The changes in the visual field have characteristic features and correspond with the basic physiopathological rules of sensorimotor induction. Changes of the visual field are usually found in the eye corresponding with the side of the disequilibrium; and only rarely, in severe cases of unilateral disequilibrium, the contralateral eye can be affected as well. In the homolateral eye the changed visual field manifests itself from the beginning as in the second and third patient, or appears increasingly in the course of successive tests as in the first patient. This depends on the degree of the basic postural impairment. In all patients the constriction begins temporally and finally assumes the form of a concentric constriction. The velocity of occurrence of the constriction also depends on the severity of the basic postural impairment. In the same patient changes of the visual field can vary and even disappear at different times depending on the changing condition of the basic motor disturbance. These findings as well as the effect of a latency period indicate clearly, as in all induced sensory phenomena, the dynamic character of this impairment of the visual field.

In addition to the fact that constriction of the visual field occurs as an induced symptom, it is of special interest that the changed field of vision may be influenced by colors. For better comprehension it should be brought to mind that the phenomenon of mutual influence of motor and sensory functions is a feature of the sensorimotor induction syndrome. Accordingly, not only motor procedures induce sensory changes, but contrarily, sensory stimuli also influence motor function. It was further shown that the effect of colors belongs to these sensory stimuli too, and has a systematic influence on the existing disturbances in these patients (7). This color effect was also found to be present in the patients discussed above with regard to changes of the visual field, in that red aggravated and accelerated the concentric constriction, while blue caused increasing widening until return to normal. This effect of colors on the visual field must not be interpreted as a direct effect of one sensory function on the other. Tests have proven that in general, and also in the patients discussed above, this color effect results primarily from its corresponding effect on the postural attitude, thereby indirectly influencing the sensory functions. The effect of colors on the visual field described above is part of a general neurodynamic mechanism which is a basic feature of the sensorimotor induction syndrome and has equal and parallel effect on other functions as well.

The findings described above are of theoretical and practical significance in connection with the diagnosis of visual defects. Apart from the two well-known disturbances of the visual field—the plain primary disturbances caused by anatomic lesions of the visual tracts on the eye itself and the concentric, mostly tubular constriction of the visual field of psychogenic origin—a third form must be taken into consideration—the dynamic change of the visual field described above. Like all other secondary disturbances of perception found in the sensorimotor induction syndrome, this dynamic change of the visual field is secondarily induced by the primarily impaired equilibrium and occurs in spite of anatomic integrity of the sensory organs concerned. The secondarily caused change of the visual field is also subject to the same dynamic rules which are valid for all secondary disturbances of perception.

Summary

In patients suffering from unilateral disequilibrium with the features of the sensorimotor induction syndrome, a characteristic change of the visual field is found. This change manifests itself by a concentric constriction of the visual field, the temporal part being more affected, and is usually found in the eye corresponding with the side of the disequilibrium. This change of the visual field becomes apparent either on successive tests or is present from the start and increases on repeated examination. The change of the visual field can be distinctly influenced by colors, red aggravating and accelerating the concentric constriction, and blue causing its retrogradation. The dynamic change of the visual field described above belongs to the secondary disturbances of perception which occur in spite of integrity of the sensory organs concerned, and which are subject to the physiopathological basic rules

of sensorimotor induction in unilateral disequilibrium.

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INCIDENCE OF FRACTURES IN CONVULSIVE THERAPIES WITH AND WITHOUT ANECTINE[1]

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Introduction

Two previous studies have been presented on thoracic spine fractures (5, 7). This is a comparison study of the incidence of thoracic spine fractures with the following groups and the two former groups as cited above. In Group I, differential cerebral stimulation (DCS) was used alone; in Group II, DCS was combined with Anectine (4–8); in Group III, DCS and insulin were combined; in Group IV, DCS, insulin and Anectine® were combined; in Group V, Metrazol was combined with Anectine; and in Group VI, various combinations of the above were employed.

A series of 257 consecutive cases with all pertinent data was surveyed. In Group I, 105 patients received DCS alone; in Group II, 76 patients received DCS with Anectine; in Group III, 11 patients received combined DCS and insulin; in Group IV, 8 patients received DCS and insulin with Anectine; in Group V, 8 patients received Metrazol with Anectine; and in Group VI, 49 patients received various combinations of the above treatments (22 of this group received Metrazol with Anectine).

Method of Study

A lateral film of the thoracic spine was obtained before and after each type of therapy. If fracture was suspected at any time during the course of therapy, suitable films were obtained to include or exclude the pathology. Due to the lack of clinical symptoms of some patients, the fracture or fractures were not discovered until the post-therapy film (2).

Of the 257 patients studied, 126 had previous shock therapy and 131 had no previous shock therapy.

The factors correlated with shock fractures were age, race, weight, height, osteochondrosis, spondylosis, kyphosis, diagnosis, previous shock history, no previous shock history and clinical improvement. (All patients were males; therefore, sex could not be correlated.)

Results

There was no relation of the incidence of thoracic spine fractures to age, weight, height, osteochondrosis, spondylosis, kyphosis, diagnosis, previous shock history, no previous shock history or clinical improvement; but it seemed to be related to race. Of the 39 fractures, 37 occurred in 219 white patients and 2 occurred in 38 colored patients. On the basis of the total sample, 6 would have been expected in the colored group.

We did not find that previous shock therapy predisposed to fractures in subsequent therapy. In the previously treated group of 126 patients, 19 fractures occurred with an incidence of 15.1%. In the untreated group of 131 patients, 20 fractures occurred with an incidence of 15.3%. Of the patients who had previous fractures only 1 had a new fracture as a result of additional treatment.

In Group I, when DCS was given alone to 105 patients or 41% of the 257 patients studied, 20 fractures occurred with an incidence of 19.05%.

In Group II, when DCS and Anectine were given to 76 patients or 30% of the 257 patients studied, 2 fractures occurred with an incidence of *2.6*%.

In Group III, when DCS and insulin were given to 8 patients or 3.1% of the 257 patients studied, 2 fractures occurred with an incidence of 25%.

In Group IV, when DCS, insulin and Anectine were given to 11 patients or 4.3% of the 257 patients studied, 2 fractures occurred with an incidence of 18.2%.

[1] Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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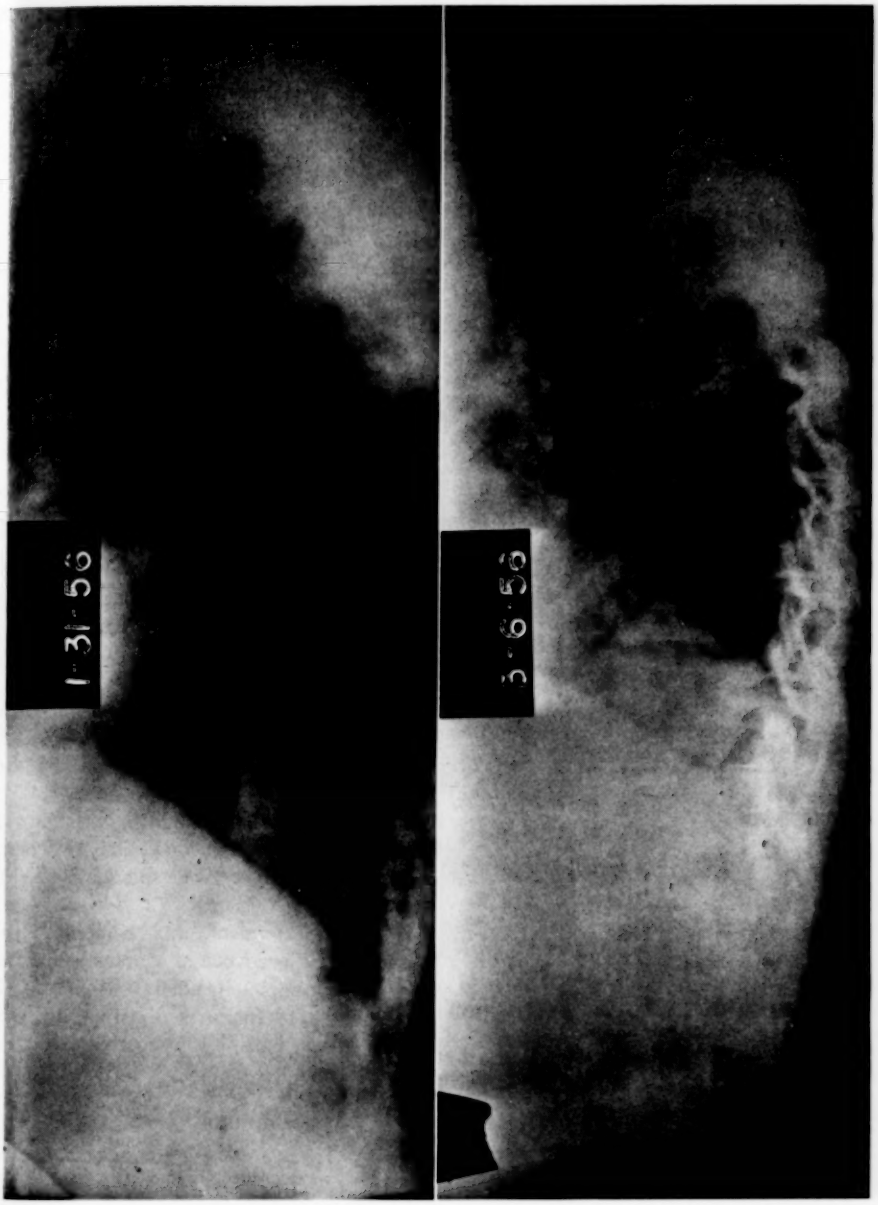

FIG. 1. Fractures of the thoracic spine in DCS shock therapy in a 28-year-old white male, 70½ in. height, weight 198 lb., with a diagnosis of schizophrenia, paranoid type.

(A) On the control film of January 31, 1956, no abnormalities were manifest. DCS with Anectine was started on 2/3/56, and 19 Stage IV comas of 1-minute duration were given.

(B) A post-therapy film obtained on 3/6/56 showed superior end-plate indentation and compression of several of the upper thoracic vertebrae, especially T-5 and 6. This is a noteworthy case, particularly due to the fact that the fractures occurred with Anectine and also that they were only found on the post-therapy film with no clinical symptoms manifested by the patient referable to the fractures.

In Group V, when Metrazol and Anectine were given to 8 patients or 3.1% of the 257 patients studied, *no* fractures occurred with an incidence of 0%.

In Group VI, when various combinations of the above types of therapy (including the 22 patients who had Metrazol and Anectine) were given to 49 patients or 19.1% of the 257 patients studied, 13 fractures occurred with an incidence of 26.5%.

Other studies of fractures of the spine using Metrazol alone have reported a high incidence of fractures (⅓ or 33%). In our series of 30 patients, when Anectine was combined with Metrazol, no fractures occurred.

In this series, in 19 patients who sustained fractures and had clinical symptoms sufficient to warrant x-ray examinations and in whom a diagnosis of fracture was made, 9 occurred in the first 5 treatments: 2 during the 1st shock treatment; 2 during the 2nd shock treatment; 1 during the 3rd shock treatment; 2 during the 4th shock treatment; 2 during the 5th shock treatment. The remainder occurred as follows: 2 during the 6th shock treatment; 1 during the 9th shock treatment; 1 during the 10th shock treatment; 1 during the 12th shock treatment; 2 during the 14th shock treatment; 1 during the 16th shock treatment; and 1 during the 22nd shock treatment. There were 20 patients whose fractures were not detected until the post-therapy film. On the average, all of the patients received 20 or more shock treatments.

TABLE 1.—THE INCIDENCE OF FRACTURES IN RELATION TO TREATMENT ADMINISTERED

Treatment Administered	Number Cases	Number Fractures	Per Cent Fractures
DCS alone	105	20	19.05
DCS with Anectine	76	2	2.6
Combined DCS—Insulin comas with Anectine used in DCS	11	2	18.2
Combined DCS—Insulin comas without Anectine	8	2	25.0
Metrazol with Anectine	8	0	0
Various combinations of above treatments with and without Anectine	49 (22)*	13 0	26.5 0
Totals	257	39	
Total per cent fractures—15.18			

* This group constitutes a large portion of the treatment combinations, but separate radiological studies before and after Metrazol with Anectine treatments revealed no new fractures nor progression of any existing old fractures.

CONCLUSIONS

1. Age, weight, height, osteochondrosis, spondylosis, kyphosis, diagnosis, previous shock history, no previous shock history or clinical improvement did not have any demonstrable bearing on the incidence of thoracic spine fractures.

2. When differential cerebral stimulation (DCS) was given alone, the incidence of thoracic spine fractures was less than when electric shock therapy (EST) was given alone (19%–33%).

3. When differential cerebral stimulation (DCS) was given alone, the incidence of thoracic spine fractures was about the same as the insulin shock therapy (IST) group alone (19%–18%).

4. When Anectine was given in combination with differential cerebral stimulation (DCS) alone, the incidence of thoracic spine fractures was reduced from 19.05% to 2.6%.

5. When Anectine was given with the various combinations of therapy, the incidence of fractures of the thoracic spine was slightly lower (25%–19%).

6. When Metrazol was combined with Anectine the incidence of thoracic spine fractures was completely eliminated (33%–0%).

7. Of the 19 fractures diagnosed by x-ray during shock, 9 or 47.4% occurred in the first five treatments.

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USE OF SUCCINYLCHOLINE CHLORIDE (ANECTINE) IN ELECTROSHOCK THERAPY

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ANGELO J. EMMA, M.D.

The introduction of convulsive therapy in psychiatry created a number of problems. Foremost among them has been the incidence of fractures, especially of the spinal vertebrae and of long bones. It is generally agreed that this is due to the violence of the induced convulsion. In addition, the muscular exertion may cause a strain on a weakened heart and be accompanied by respiratory complications. To reduce or eliminate these side effects as well as the threat of malpractice suits, new electroshock machines with various currents and different muscle relaxants have been recommended.

Curare and "curare-like" drugs such as flaxedil and decamethonium have been used. However, they were quite disappointing because of their prolonged action, the delayed respiratory recovery, and the histamine-like side effects of some. Furthermore, in patients in whom complete muscle relaxation was necessary because of existing skeletal pathology, the large doses made the treatment more hazardous because of prolonged apnea and cyanosis. When these patients also had some cardiovascular or respiratory pathology, the prolonged apnea added to the risk of the treatments considerably. Even sufficiently large doses of curare were not able to eliminate fractures entirely, as reported by Meschan and co-workers (7).

Succinylcholine is the first ultrashort acting muscle-relaxing drug with very low toxicity. The muscular relaxation achieved with anectine is far more complete than that achieved with a very large dose of curare. Such large doses of curare, moreover, would render the treatment extremely dangerous. It is therefore no surprise that anectine has been widely accepted as the best muscle relaxant presently available. Most psychiatrists follow the generally accepted rule of administering pentothal or some other barbiturate anesthesia in conjunction with succinylcholine in electroshock therapy, thus creating a possible synergistic or antipathic effect between the drugs. We feel that the disadvantages outweigh the advantages in using pentothal anesthesia with anectine. Electroshock itself depresses the respiration centrally; the added barbiturate increases this depressing effect and therefore either creates or increases the post-convulsive apnea. Further difficulties must be anticipated by the peripheral respiratory depressant action of anectine.

Wilson and Nowill (12) reported a patient who had a prolonged apnea lasting for about ten minutes following an electroshock treatment which was facilitated by pentothal and anectine. Alexander and co-workers (1) mention one patient whose apnea persisted for 18 minutes after an electroshock treatment, which they had administered with an apparatus utilizing unidirectional current in conjunction with pentothal and anectine. Gould (3) and Harper (4) reported prolonged apnea lasting up to three hours following the use of pentothal and anectine in connection with electroshock therapy. Prolonged apnea may be harmful to the cardiovascular system, in spite of the decreased strain achieved by muscle relaxants. Kalinowsky (6) who dislikes any modified electroshock warns that intravenous barbiturates increase the risk of the treatment when given in association with muscle relaxants. He also noted that respiratory difficulties are greater in such patients than in those treated without barbiturates.

Pentothal was responsible for certain complications which did not recur when omitted during the following electroshock treatments. There are apparently a small number of patients who are extremely sensitive to pentothal, even when it is given in very small amounts, highly diluted and injected very slowly. Patients treated with only anectine recover from the electroshock faster and the treatment itself is much shorter, lasting about one-half to one-third the time needed for the combination. The amount of anectine needed for complete

muscular relaxation was much smaller when anectine was used alone, than when given in combination with pentothal.

Heretofore, pentothal anesthesia had been considered a necessary adjunct to the administration of anectine in electroshock treatments in order to eliminate the unpleasant effects of succinylcholine, such as muscular fasciculations, feelings of suffocation and general paralysis. It is true that these are frightening and unpleasant experiences for the conscious patient undergoing electroshock treatments. However, utilizing Impastato's technique as related to us by Padula (10), we were able to overcome the subjective feelings of the patient receiving anectine without using pentothal anesthesia. The following case histories will illustrate the points of discussion.

A 51-year-old white married man received 23 electroshock treatments modified by pentothal anesthesia and anectine. One hundred and fifty to 200 mg. of pentothal and approximately 25 mg. of anectine were used. On five occasions, endotracheal intubation was necessary because of prolonged apnea and severe cyanosis. Later, pentothal was omitted, and the dose of anectine was reduced gradually. He had 10 more treatments with anectine alone (10–12 mg.). He had better muscular relaxation with the smaller amount of anectine and immediately started breathing spontaneously after the end of the convulsion.

A 63-year-old widow had received 12 electroshock treatments with 150 mg. pentothal and 15 mg. anectine. Following each treatment she had prolonged apnea and cyanosis. When pentothal was omitted during the following eight treatments, she had the same muscular relaxation with only 10 mg. anectine, and there was no evidence of prolonged apnea.

A 25-year-old married woman weighing approximately 200 lb. received eight electroshock treatments modified by the use of 150 mg. pentothal and 15 mg. anectine. Each treatment was followed by prolonged apnea. When given anectine alone during the next 10 treatments, she had the same muscular relaxation with 8 mg. anectine, and there was no evidence of prolonged apnea.

One patient who received 150 mg. pentothal and 10 mg. anectine developed a severe rash and angioneurotic edema during one electroshock treatment. Upon omission of pentothal, the patient had no recurrence of the above symptoms during the next three treatments, which were modified by anectine alone.

Steven and co-workers (11) reported one patient who vomited immediately upon induction of pentothal anesthesia. Part of this vomitus was aspirated, but pulmonary edema developed, and the patient died five hours after this electroshock treatment.

In the literature available to us, only two psychiatrists have been using anectine in electroshock therapy without a barbiturate anesthesia. Murray (8) reported a series of approximately 750 patients to whom he gave electroshock without pentothal anesthesia and was thus able to use smaller doses of anectine. Murray informed his patients of "twitching sensations" that they were going to feel during the anectine-softened electroshock treatment. He then also reassured them that they would fall asleep soon. He administered the electroshock 10 seconds after the onset of facial twitching. Murray mentioned in his report that none of the patients had any recollection of the treatment, and that none objected to further electroshock.

Glover and Roisum (2) also recommended the use of anectine in electroshock without any pre-medication. They were using 10–20 mg. of anectine injected rapidly into the vein of the patient. These authors waited until evidence of twitching of facial muscles and/or respiratory embarrassment started before administering the electric stimulus. In the approximately 1,000 treatments they reported they gave the electric treatment usually between 5 and 60 seconds after the end of the anectine injection. Glover and Roisum admitted that their patients frequently complained of unpleasant subjective sensations associated with the injection of anectine.

We used anectine to produce muscular relaxation in 181 patients who received a total of 1,561 electroshock treatments. The group consisted of 127 females (70%) and 54 males (30%). The ages of the patients ranged from 17 to 79. Seventy-six patients (42%) suffered from a manic-depressive psychosis; 67 patients (37%) suffered from schizophrenia; and 38 patients (21%) suffered from involutional psychosis.

The group of patients included one woman of 79 years of age who accidentally fell and suffered a comminuted fracture of the lower end of the right ulna and radius about five weeks before her first electroshock treatment.

One 50-year-old man suffered from Marie-Strumpell's Disease and was bent over because of the pathology of his spine. One 65-year-old woman suffered from advanced diffuse Paget's Disease which also involved the pelvis and both femora. This patient was previously re-

fused electroshock because of the above condition. One 63-year-old man suffered from compression fractures and wedging of four of the mid-dorsal vertebrae (D5-8) with secondary marked kyphosis. In addition, his x-ray also revealed narrowing of the L2, 3, 4 intervertebral disc spaces. The body of L5 showed appreciable compression with decrease of its vertical diameter. The changes in the spine were due to previous shock treatment.

In addition, there were many others among our patients who showed evidence of compression fractures from previous shock therapy, advanced osteoarthritic changes or osteoporosis which disabled them partially. Our series also included patients with a history of coronary thrombosis three or more months prior to shock therapy, bundle branch block, and some patients with coronary insufficiency. One 54-year-old woman had a bicuspid aortic valve with a very large ventricle and mitral and aortic insufficiency.

The following is the description of the technique used by us:

The patient is placed on the bed without hyperextending his spine. To add to the patient's comfort, a pillow is usually put under his head. Then $\frac{1}{100}$ mg. to $\frac{1}{50}$ mg. of atropine is given intravenously. A 22-gauge needle is used to facilitate rapid injection of anectine that follows later. The syringe is then removed from the needle, and another syringe containing 5 mg. to 20 mg. succinylcholine is connected to this needle and injected as rapidly as possible. Ten to thirteen seconds after completion of the injection of anectine, a subthreshold electric stimulus to produce a petit-mal reaction is administered. The patient instantly becomes confused and unconscious. Approximately 20 seconds after the first stimulation, a second stimulus is administered. This electric stimulation produces a very soft grand-mal reaction which is hardly noticeable and can often be detected only by palpation of the extremities or watching the face for the rhythmic contractions of the eyelids. Many patients start breathing spontaneously immediately after the end of the convulsions, obviating the use of oxygen. In most instances, we use 100 per cent oxygen routinely either by resuscitation or by positive pressure until the return of the patient's own respiration.

It was never necessary to insert an endotracheal tube in any of our patients who received anectine alone. Yet, in some instances where anectine and pentothal were used, intubation had to be employed. Nevertheless, it is advisable that a suction device, pharyngeal and tracheal tubes should be in readiness in order to insure a free airway at all times.

In using pentothal anesthesia with anectine, it is important to use an anesthetist in order to deal with respiratory complications and emergencies that may arise. There are some therapists who have acquired sufficient skill in anesthetic procedures to give these modified treatments without the assistance of an anesthetist. With the above mentioned technique respiratory complications did not occur. We gave the treatments without the assistance of an anesthetist.

The dosage of anectine has no relationship to the body weight, but rather to the amount of muscle strength present. We usually administer 10 mg. anectine to women and 15 mg. to men for the first electroshock treatment. If more muscular relaxation is achieved than desired, or if the patient shows some apnea following the treatment, we reduce the amount of anectine for the next electroshock treatment. In some instances the dose of anectine can be reduced in subsequent treatments, suggesting the possibility of an increasing sensitivity to the drug. In the presence of severe skeletal changes such as cases of recent fractures or Paget's Disease or Marie-Strumpell's Disease, etc., we increase the amount of anectine by 5 mg. for the first treatment. The dosage of anectine used in our patients ranged from 4 mg. to 22 mg. Occasionally we noted that a certain vial of anectine did not produce sufficient muscle relaxation during the treatments. Upon investigation we were able to discover that some vials of anectine were kept at room temperature for long periods of time, thus reducing the efficacy of their contents.

If all or part of the anectine had been injected paravenously by accident, it is advisable not to proceed with the treatment but rather to repeat the injection in about three to five minutes. Holmberg and Thesleff (5) reported a patient who suffered a compression fracture of the third and fourth thoracic vertebrae during an electroshock treatment owing to the fact

that part of the anectine was given paravenously. Murray (9) also reported a similar complication due to the accidental injection of anectine subcutaneously.

There is no need to use a mouth gag as long as the mouth is kept closed by supporting the lower jaw during the treatment. However, on some occasions we used a plastic sponge, wrapped in a piece of gauze, which is placed between the teeth and the lower jaw held against it.

All the electric shock apparatus available in the hospital produced the desirable responses equally well. However, it was easier to obtain the petit-mal response when the electric stimulus could be automatically timed.

This method overcomes the subjective discomforts associated with the use of anectine without the necessity of a barbiturate anesthesia. It eliminates or greatly reduces the post-convulsive apnea. Anectine does not alter the beneficial effect of electroshock. The dose of succinylcholine could be markedly decreased in the absence of pentothal anesthesia with equal or better relaxation than when pentothal and anectine were used together. There were no complications in our series of treatments.

We were able to treat patients with severe skeletal and cardiovascular pathology whose physical condition previously contraindicated electroshock treatments. This method enabled us to treat a larger number of patients since only one-half or one-third of the time is needed to carry out the entire treatment procedure as would be needed with the use of pentothal and anectine combined. Finally, this method reduces or eliminates the threat of malpractice suits.

Summary

Anectine has been used to produce muscular relaxation in 181 patients who received 1,561 electroshock treatments. The advantages of using anectine alone instead of in combination with pentothal anesthesia are discussed. A method is described which eliminates the unpleasant effects of anectine. An electric stimulus is applied that causes a petit-mal reaction of which the patient has no recollection and which stuns the patient so that he does not feel the effect of the anectine. This method appears safe and useful, and its use is therefore recommended.

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THE RECURRENCE OF SEIZURES IN TIME[1]

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In the establishment of correlations between neural and behavioral events, seizure phenomena are an excellent vehicle. They are fairly well-defined sets of behaviors whose occurrence is accompanied by disturbances in the electrical rhythms of the brain. The behaviors emitted during seizures are also often of localizing significance in determining the site of brain lesions. If behavior with such well-defined neural correlates can be shown to exhibit lawfulness from the standpoint of behavior theory, important progress may be made in explicating the neural mechanisms of behavior and in increasing understanding of the dynamics of neural action and of the laws of behavior themselves. This present study is the first of a series of attempts to determine whether seizures as such do exhibit lawfulness from a behavioral point of view.

Hull (1, p. 10) has theorized that the probability that any response which has once occurred will recur as the next term in a response chain is an inverse function of the number of successive responses in which it does not occur. In a similar vein, Zipf (4, pp. 40–47) has shown that the probability of recurrence of any word that has once been emitted declines hyperbolically as the interval in which that word does not occur increases in magnitude. Generalization of this Zipfian interval-frequency relationship to seizure phenomena leads to the prediction that if the intervals of time between successive seizures are arranged in order of increasing magnitude, there should be an inverse hyperbolic relationship between the size of an interval and the frequency with which intervals occur. Seizures should tend to cluster in time, and the extent of such clustering should determine the rate at which seizures occur.

PROCEDURES AND RESULTS

To test these hypotheses, all of the seizure records for April, 1955, at the Indiana Village for Epileptics[3] were divided up according to the total number of seizures recorded for that month. The intervals between successive seizures were determined, and all groups not having a total of 50 intervals were eliminated from consideration. Table 1 summarizes the seizure frequency groups used, together with the number in each group and the total aggregate of seizure intervals obtained by each group.

As the groups were assembled without regard to sex, it was necessary to demonstrate that the seizures of females did not tend to cluster any more than did the seizures of males. The literature on the subject (e.g., 2, p. 23) contains many references to the effect that among females seizures tend to cluster around the time of the menstrual period. To this end, the group having 5, 6, 8, 9, and 10 seizures was divided up by sex, and the resultant distributions of seizure intervals were dichotomized arbitrarily at an interval of two days. The significance of differences in clustering was tested by Chi^2, and none of the differences was significant or showed any tendency to favor one sex over the other. It seemed apparent, therefore, that the seizures of females did not tend to cluster any more than did the seizures of males, and the sexes could be combined into the same groups.

In order to test whether seizures tended to cluster in time more than might be expected by chance alone, 100 possible distributions of seizures in a 30-day period were set up for each seizure frequency by means of a table of random numbers. The proportions of intervals of two days or less which occurred within each hypothetical seizure frequency group were determined, and these values were smoothed by fitting a least-squares curve to the data showing the regression of these proportions on their respective hypothetical seizure frequencies. These smoothed values and the proportions of actual seizure intervals which occurred within a two-day period are shown in table 2. It can be seen that only in the

[1] This paper was presented in part at the meeting of the Midwestern Psychological Association, St. Louis, May 3–5, 1956.

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TABLE 1.—SEIZURE RATE GROUPS USED IN THIS STUDY TOGETHER WITH THEIR FREQUENCIES AND TOTAL NUMBER OF SEIZURE INTERVALS

Seizures in April, 1955	Number in Group	Total Seizure Intervals
2	80	80
3	57	114
4	45	135
5	35	140
6	28	140
8	14	98
9	10	80
10	9	81
11	5	50
18	3	51
21	3	60
25	3	72

TABLE 2.—EXPECTED AND OBTAINED PROPORTIONS OF INTERVALS OF 2 OR LESS DAYS IN THE DISTRIBUTIONS OF SEIZURE INTERVALS FOR EACH OF THE SEIZURE RATE GROUPS

Seizures per Month	Expected Proportion	Obtained Proportion	Significance of Differences
2	.16	.28	.01
3	.22	.40	.01
4	.28	.43	.01
5	.34	.45	.03
6	.40	.50	.02
8	.51	.59	—
9	.55	.64	—
10	.58	.62	—
11	.61	.80	.01
18	.78	.79	—
21	.83	.83	—
25	.91	.87	—
Over-all significance			.01

groups with 21 and 25 seizures, respectively, did the calculated proportions equal or exceed the actual proportions of seizure intervals. When the over-all significance of the differences between the two groups is tested by means of Wilcoxon's test for paired replicates (3), more seizures are found to cluster than would be expected by chance. This is significant at the .01 level. When the obtained proportions are contrasted with the expected proportions, six out of twelve are significant at the .03 level or better.

Having established that seizures do tend to cluster in time, the next task was to determine whether the regression of the frequency with which seizure intervals occurred upon the size of the seizure intervals was inversely hyperbolic. The intervals and their frequencies were converted into logs, and the least-squares slopes of the resulting distributions were calculated. Inasmuch as a hyperbola becomes a straight line in a doubly logarithmic transformation, the extent to which the obtained distributions differed from a straight line relationship was tested by Chi^2. These data are presented in table 3. The inverse nature of the relationship is testified to by the fact that all the slopes are negative. The median slope of -1.13 is not significantly different from a slope of -1.00 which is the slope characteristic of an equilateral hyperbola. The Chi^2 test for the linearity of the distributions suggested that none of the groups differed significantly from a rectilinear relationship and all but the group with 9 seizures were significantly the same as a rectilinear relationship. The data suggest therefore that the probability of recurrence of seizures is an inverse hyperbolic function of time.

If the degree of clustering is related to the seizure frequency, the correlation between seizure frequency and the proportion of the total number of seizure intervals accounted for by any given interval should be maximal for the shortest intervals and decrease as the length of the intervals increases. To test this, the proportion of the total number of seizure intervals accounted for by each interval was computed for each of the seizure frequency groups. A rank difference correlation was computed between these proportions as contained within the 10 shortest intervals and the absolute seizure frequencies. It was predicted that the highest positive correlations would be found among the shortest intervals. The correlations should decrease and then become negative as the shortest distributions began to exhaust themselves. These correlations are presented in table 4. The groups with 21 and 25 seizures were eliminated from this comparison as they only contained five and six different magnitudes of intervals, respectively. The trend in the correlations fulfills the prediction and suggests a critical period of three days for the recurrence of seizures. If a patient can be kept seizure-free for three days, then he is apt to go for an even longer period without seizures.

TABLE 3.—The Slopes of the Doubly Logarithmic Transformation of the Interval Frequency Curves in the Various Seizure Rate Groups and the Chi² Test of their Linearity

Seizures per Month	Slope	df	Chi²	P
2	−.52	27	3.37	>.99
3	−.89	21	2.57	>.99
4	−.80	17	1.08	>.99
5	−.91	14	0.95	>.99
6	−1.16	18	1.48	>.99
8	−1.21	14	1.21	>.99
9	−1.10	10	9.67	appr. .47
10	−1.23	9	0.58	>.99
11	−1.27	9	1.92	>.99
18	−1.49	8	0.55	>.99
21	−1.08	4	0.29	>.99
25	−1.62	5	0.25	>.99
Median slope....	−1.13			

TABLE 4.—Rank Order Correlations (Rho) between Seizure Rates and Proportion of Total Seizure Intervals Included within Each of the Ten Shortest Intervals (excluding Groups with 21 and 25 Seizures)

Number of Days between Seizures	Rho
0	.87*
1	.95*
2	.76*
3	.41
4	−.19
5	.35
6	−.56†
7	−.34
8	−.63†
9	−.30

* ρ is at least .01.
† ρ is at least .05.

TABLE 5.—Rank Correlations (Rho) between Seizure Rates and Proportion of Intervals Occurring within Each Successive Corresponding Area of the Interval Frequency Curves When All Curves Have Been Divided into 5 Corresponding Areas

Area	Rho
I	.99*
II	.70†
III	.56†
IV	.22
V	.31

* ρ is at least .01.
† ρ is at least .05.

To control for the possibility of artifact, all distributions were divided into five equal intervals, and the proportion of seizure intervals contained in each successive area correlated with the absolute seizure frequencies by means of a rank-difference correlation. It was predicted that the correlations would move from high positive to low positive since the differing number of intervals in each seizure frequency group was now controlled. Table 5 presents these data and suggests that the hypothesis is upheld.

Discussion

In evaluating the findings of this study, it should first be noted that the observation that the seizures of men and women cluster to the same degree does not imply that the seizures of females do not cluster around the time of the menstrual period. It only implies that while menstruation may be a specific occasion associated with the occurrence of seizures in females, there are as many occasions which may induce seizures in males as in females.

The data of this study can be accounted for neurologically if one postulates that overt behavior appears when the number of nerve cells involved in mediating some overt behavior reaches some critical level. If one postulates a few hyperexcitable cells linked, perhaps, in some sort of reverberating circuit, the pattern of excitation would tend to spread probabilistically as other neurones become or cease to be available for excitation. When the number of neurones involved reaches some critical point, overt seizure behavior appears which continues until enough cells become exhausted so that the number of neurones involved falls below the critical level. The same random process takes place below this limen, and the probablilty of recurrence of overt seizure behavior depends on the number of neurones still involved in the seizure process.

The specific behaviors noted in any given seizure occurrence are, of course, a function of the behaviors mediated by the nerve cells involved. The random fluctuations of excitation should be echoed by fluctuations in the behaviors available to the clinical observer. The spread of excitation in the neuronal net should produce distinct sequences of involvement of CNS functions which should depend

in part on the number of cells mediating these functions and in part on the availability of these cells for inclusion in the seizure process. The distance of these cells from the original focus of excitation is probably an important variable in this connection.

The critical number of neurones necessary to convert seizure activity from microscopic to macroscopic levels is not an absolute affair, but is relative to the number of neurones subserving any particular function. Functions which are served by large numbers of neurones should be ralatively less prone to disruption by seizure activity. "Minor" seizures, such as auras or transitory and minimal losses of consciousness, should be more common than "major" ones. "Major" seizures should more frequently tend to terminate a sequence of seizures since more of the nerve cells which would be involved in the seizure process are apt to be in a refractory phase and not as easily stimulable.

From the standpoint of seizure management this study also carries the implication that any time a seizure is prevented from occurring, a number of additional seizures is prevented. Since seizure frequencies seem to be related to the degree to which seizures cluster in time, maximal precautions after the occurrence of any seizure, however slight, should be rewarded by marked decline in seizure frequencies. Since the critical period for the recurrence of overt seizure activity seems to be within three days of a previous occurrence, great care should be exercised for at least this period of time.

Summary

Analysis of the seizure records at the Indiana Village for Epileptics to determine the distribution of the recurrences of successive seizures in time suggests that seizures tend to cluster in time. In spite of the fact that seizures in females may be precipitated by the menstrual period, there seems to be not greater tendency for seizures in females to cluster any more than do those in males. The probability of occurrence of a second seizure after one has already occurred seems to be an inverse hyperbolic function of time. The degree to which seizures cluster in time is related to the over-all seizure frequency. The critical period for the recurrence of seizure activity is about three days.

These data are accounted for by a hypothesis that a probabilistic spread of excitation from a group of hyperirritable cells which comprise a seizure focus takes place. Overt seizure activity occurs when enough neurones become involved in the seizure process. The extent to which any function is involved depends upon the number of cells governing that function and the distance of these neurones from the original seizure focus. These factors determine the temporal sequences of involvement of functions during a seizure.

From the point of view of management, this study carries the implication that every time a seizure is controlled, a whole sequence of seizures is rendered less probable. Major precautions taken after any instance of seizure activity, however mild, should reduce materially the over-all frequency of seizures.

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THE EFFECTS OF FRENQUEL UPON CHRONIC DISTURBED PATIENTS[1,2]

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History and Introduction

Frenquel, or alpha-(4 piperidyl) benzhydrol hydrochloride, is a relatively new drug which has been attributed with the property of blocking schizophrenic hallucinations and delusions and leading to better ward adjustment. A review of the literature concerning the effects of this drug upon patients of several diagnostic categories reveals marked inconsistencies in the data.

It has been reported (4) that Frenquel was less effective than reserpine and Thorazine in treating chronic paranoid patients. On the other hand, it was found (1, 2) to be effective in the dissociation syndromes and in blocking the development of LSD-25 and mescaline psychoses, but ineffective in the psychotic depressive states, obsessive-compulsive disorders, and anxiety reactions. Frenquel was seen (6) to correct the schizophrenic-like changes in the EEG patterns of rabbits produced by injections of LSD-25 and mescaline, but it did not correct similar EEG changes induced by such drugs as DFP, amphetamine, and pipradol. Frenquel is reported (3, 5) to be effective in eliminating delusions and hallucinations in acutely psychotic patients, but it is much less promising in patients with chronic disorders.

Most of the investigations performed suffer from a lack of objective criteria and adequate controls. The experiment most pertinent to the present study is one of the few experiments which incorporated control groups (7). Thirty-nine chronic disturbed patients whose average period of hospitalization was 17.5 years were studied. After clinical evaluation according to 9 selected criteria, both the experimental and the control groups received placebo during the first period of 4 weeks; Group I was given Frenquel during the second period while Group II remained on placebo; Group I was returned to placebo during the third period while Group II was placed on Frenquel; and both groups received placebo during the fourth period. The results reported were that 21 of the 39 patients showed definite improvement during the period in which they received Frenquel and some improvement was noted in 7 others. Twenty-six returned to their pretreatment level when they were again given placebo. With respect to ward adjustment, 21 were improved and three were worse. Hallucinations and delusions diminished in intensity in only 5 of the 39 patients. There were no deleterious side effects.

In a previous study of 40 patients at this hospital, in which 20 received Frenquel for one month and 20 received placebo for one month, the Frenquel group was found to be significantly worse in hospital adjustment as measured by the Hospital Adjustment Scale by Ferguson, McReynolds, and Ballachey. This scale evaluates communications and interpersonal relations, care of self and social responsibility, and work activities and recreation. The total score is a measure of the extent to which behavior reflects an "expanding" or a "contracting" personality. The results of this experiment were questionable since the patients were assigned at random to the two groups, and, by chance, the Frenquel group had a mean score which was significantly higher than that of the placebo group at the beginning of the study. It is possible, therefore, that this finding could have resulted from mere regression toward the mean, and so a new study was undertaken. In addition, information concerning the effect of the drug upon the patient's delusions and hallucinations was desired.

Subjects

Sixty-six female chronic patients were selected by ward attendants as possible hallucinators, and all of these were interviewed by two psychologists. Of the 66 patients, 21 were

[1] The Frenquel and the placebo used in this study were supplied by the Wm. S. Merrell Company, Cincinnati 15, Ohio.

[2] This study was undertaken at Eastern State Hospital, Williamsburg, Virginia.

rejected for lack of clear evidence of hallucinations from the patients themselves and 7 refused to take the pills. This left a total of 38 patients on four different wards.

Method

The charge attendant on each of the four wards was given careful instructions on the administration of the Hospital Adjustment Scale (H.A.S.). The attendants then rated each subject on the H.A.S., and, on the basis of those scores, the patients were divided into two groups with nearly equal group means (29.89 and 29.80). A psychologist who had no part in the interviews or the evaluations equated the groups, and only she and the pharmacist had knowledge of which patients received Frenquel and which ones were given placebo. No other tranquilizing drugs or therapy was given during the experimental period. There was no difference in appearance, taste, or odor between the Frenquel and the placebo pills. Approximately one-half of the patients in each ward were in each group. The 20 patients in the Frenquel group received 20 mg. of Frenquel in pill form three times a day for one month. The 18 patients in the placebo group received the placebo pills three times a day for one month. At the end of that month, all of the patients were again interviewed by the same examiners, and the H.A.S. was readministered to each patient by the same attendants. Each patient continued to take the pills until the final H.A.S. and the final interviews were completed.

Results and Discussion

Of the 20 patients in the Frenquel group there were only two from whom the examiners were unable to elicit hallucinations during the final interview. These two patients retained their delusions, however. Further, the examiners felt that the delusions and hallucinations of eight of the subjects actually were more intense although a simple increase in the patients' expression of their delusions and hallucinations may have accounted for the perceived change. Of the 18 patients in the placebo group, one showed slight decrease in the intensity of delusions and hallucinations. The interviewers felt that six were worse, but the same restrictions apply here as with the Frenquel group. No deleterious side effects were observed.

The mean total H.A.S. score for the Frenquel group changed from 29.80 before treatment to 32.25 after treatment. The mean total H.A.S. score for the placebo group changed from 29.89 to 40.94 after treatment. *T-tests* were performed to determine the level of significance of difference between these means. The results of this operation are reported in table 1. There was no significant difference between scores for the Frenquel group before and after administration of the drug, nor between scores for the Frenquel group and the placebo group after administration of the pills. However, the difference between scores for the placebo group before and after administration of the pills was significant at the 1% level of confidence, i.e., only one time in one hundred cases could so large a difference occur by chance alone.

There is some evidence to suggest that this latter finding is an artifact of the rating technique employed. One rater, who scored 10 of the 18 placebo patients and only 6 of the 20 Frenquel patients, appears to have consistently "up-rated" her patients on the second adjustment scale. The Frenquel patients as well as the placebo patients rated by that person showed the greatest mean improvement. If the Frenquel patients rated by that person are eliminated from the analysis of the data, there is still no significant differences between the scores before and after medication, but the trend is toward impairment ($T = -0.61$ with 13 d.f.) rather than toward improvement. It would not be meaningful to perform this kind of analysis on the placebo group since she rated over half of the patients in that group, and the number of subjects would be too small. No such artifact could be discovered on the first H.A.S. or in the former study in which the placebo

TABLE 1.—T-Tests on Total Scores from the Hospital Adjustment Scale

	T	d.f.	P
Frenquel (before vs. after)	+0.66	19	$<.10$
Placebo (before vs. after)	+3.12	17	$>.01$*
Frenquel vs. placebo after	+1.11	36	$<.10$

* Indicates significance at the 1% level of confidence.

group was unchanged while the Frenquel group was significantly worse.

The statement which can be made with assurance from these data is that Frenquel did not improve the ward adjustment of the patients in this study. Neither did Frenquel eliminate the delusions and hallucinations of the patients studied.

Conclusions

1. Frenquel, given in divided doses totalling 60 mgm. daily, did not significantly decrease delusions and hallucinations in this study.

2. Frenquel did not significantly improve ward adjustment in this experiment.

3. Frenquel appears to have no advantageous effect upon chronic female patients in this hospital, and there are suggestions that it may decrease inhibitory tendencies among some hallucinating patients. The question of whether the drug actually has a negative effect upon ward adjustment, as indicated by the earlier study, requires further investigation.

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A CLINICAL EVALUATION OF FRENQUEL[1]

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Since previous research with mescaline and LSD-25 intoxications in man suggested that a chemical antagonist to these compounds might be useful in the treatment of schizophrenia, Fabing's announcement that the gamma isomer of Meratran (Frenquel) inhibited experimental mescaline and LSD-25 psychoses aroused considerable interest in this drug (1). Shortly thereafter Fabing and his coworkers (2) and other investigators (3, 4) reported that Frenquel was valuable in the treatment of acute schizophrenic psychoses in which delusions and hallucinations were the predominant symptoms. These reports indicated that Frenquel is an interesting drug, and that extensive clinical trials with it are warranted.

Scope of Study

Frenquel was prescribed for 44 men and 56 women between the ages of 14 and 84. In this group there were 48 acute schizophrenic reactions, 32 chronic schizophrenic reactions, 6 senile confusional states, 6 schizo-affective reactions, 4 toxic psychoses, 5 obsessive-compulsive neuroses, and 1 anxiety neurosis. They were administered Frenquel orally and intravenously from a minimum of one week to a maximum of one year. The average duration of treatment for the acute psychotic states was one month and for the chronic psychoses and neuroses six months.

Dosage

In an effort to establish the therapeutic dose of Frenquel there was considerable experimentation with dosage and route of administration in this study. The minimum oral dose was 20 mg. daily, and the maximum was 800 mg. daily. The average oral dose was 100 mg. daily. Intravenous Frenquel was used for very acutely disturbed schizpohrenic reactions and the toxic psychoses. The usal dose was 100 mg. intravenously every four hours for an average of six injections. The highest single intravenous dose was 300 mg.

Side Effects

Frenquel is a very safe drug. No serious side effects or physical complications were encountered in this investigation. One woman developed a maculopapular rash over the back which disappeared when Frenquel was discontinued. This rash reappeared when this patient subsequently was retreated with Frenquel necessitating the termination of treatment with this drug.

Therapeutic Results

The therapeutic results obtained with Frenquel in this group of patients are very difficult to evaluate. It can be forthrightly stated that this drug is not specific for the treatment of schizophrenia. This agrees with the findings of Fabing (2). There were a few patients who were helped in a dramatic fashion. These were acute schizophrenics whose illness was of recent origin and whose symptoms curiously resembled mescaline and LSD-25 intoxications with auditory hallucinations predominating. Otherwise in the majority of acute and chronic schizophrenic reactions and the schizo-affective reactions, Frenquel did not appear to have any therapeutic action.

Frenquel benefited the six senile patients in this study. Their illness was characterized by confusion, disorientation, and hallucinations. In three of these patients the symptoms appeared after major surgery for genitourinary or orthopedic reasons. In each case, intravenous Frenquel produced a prompt remission. The other three patients' symptoms appeared during convalesecnce from acute medical illnesses. The response to Frenquel in these patients was not as dramatic although the end result was good, perhaps because they received Frenquel orally.

An 84-year-old man underwent orthopedic surgery for the correction of a hip fracture. In the post-opera-

[1] Frenquel supplied by The Wm. S. Merrell Company, Cincinnati, Ohio.

tive period he developed a psychosis characterized by a progressive impairment of memory, confusion, erratic behavior, paranoid delusions, auditory hallucinations and insomnia. For one week he was given oral Frenquel, 100 mg. daily. Because he was unimproved, Frenquel was increased to 300 mg. daily, and this caused a complete remission from his psychosis within ten days. Three months later this patient had a similar psychotic episode. He was re-treated with oral Frenquel, 400 mg. daily, and within five days was symptom free.

This 72-year-old man developed an acute confusional psychosis one week after genitourinary surgery. He was extremely apprehensive and expressed a variety of paranoid delusions. He was disturbed by vivid visual hallucinations of lights, geometrical figures, dwarf animals, and threatening human figures. He also mentioned fleeting auditory hallucinations. Barbiturates and chloryl hydrate had no effect on him. One day later he was started on Frenquel, 100 mg. intravenously every four hours. After the third intravenous injection he was calm, partially oriented, and denied hallucinations. He received three additional intravenous injections of 100 mg. Frenquel in the next twelve hours. The next day he was dramatically improved, and oral Frenquel, 100 mg. q.i.d., was prescribed. On the third day he was fully recovered from his psychosis, and Frenquel was discontinued.

The most favorable and satisfactory results with Frenquel were obtained in the toxic psychoses. However, it cannot be asserted with absolute certitude that the results obtained in these patients can be attributed to Frenquel alone, since it is possible that the symptoms would have remitted without special treatment. Nevertheless, the toxic psychoses responded dramatically and apparently more rapidly when treated with Frenquel than would be expected normally.

A 20-year-old man receiving large doses of Thorazine for a chronic schizophrenic reaction developed a toxic psychosis with confusion, disorientation, and visual and auditory hallucinations. He was restless but not very apprehensive. He brushed insects off the bed sheets. He got out of bed repeatedly to seize imaginary objects on the walls and floor. He responded to hallucinations that were suggested to him. He was confused and disoriented for time and place. His attention span was very brief. He could not sleep and ate only when urged to do so. Despite these symptoms, he was mildly elated and friendly.

After 36 hours this patient was given Frenquel, 100 mg. intravenously and 100 mg. orally. Within an hour he was calm and denied hallucinations. He slept for eight hours. When he awakened, he was somewhat confused but not hallucinated or disoriented. He was placed on Frenquel, 100 mg. t.i.d. Two days later he was fully recovered.

A Wechsler and Rorschach were administered to this patient at the height of his toxic psychosis (table 1). His Verbal I.Q. was 94, Performance I.Q. 65, and Full Scale I.Q. 78. The Full Scale I.Q. was considered "spuriously low because of the great evidence of organic pathology throughout the test." Digit Span, Arithmetic, and Similarities subtest scores were significantly below the mean. Object Assembly, Picture Completion, and Block Design scores were significantly below the mean. Object Assembly, Picture Completion, and Block Design scores were significantly low also indicating a visual motor disturbance characteristic of organic disease. The deterioration index was 32 per cent.

TABLE 1.—WECHSLER TEST RESULTS

Subtests	Toxic Psychosis* WTS	Next Day† WTS
Digit span	4	9
Arithmetic	3	9
Similarities	6	11
Picture completion	3	10
Block design	5	12
Object assembly	2	8
Digit symbol	9	13
Verbal Scale I.Q.	94	105
Performance Scale I.Q.	65	104
Full Scale I.Q.	78	106
Deterioration index	32%	0%

* Due to chlorpromazine.
† After Frenquel, 500 mgm.

The Rorschach disclosed schizophrenia with paranoid features with considerable signs of organic damage. During both tests the patient frequently lapsed into "daydreaming" and his attention span was very limited.

The next day, after the patient had had a total of 500 mg. Frenquel, the Wechsler revealed a Verbal I.Q. 105, Performance I.Q. 104, and a Full Scale I.Q. 106. The discrepancy between the Verbal and Performance I.Q.'s of the previous day was no longer present. High scores were obtained on the Digit Symbol, Block Design, Digit Span, and Similarities subtests. Object Assembly was a little low, indicating very slight visual motor impairment. The deterioration index was 0 per cent. The patient was in good contact, did not daydream, and his attention span was normal.

Three other chronic schizophrenics, one man and two women, also had a similar toxic psychosis—two during Thorazine therapy and one from Pacatal. Each was treated with Frenquel in the manner described above, and each promptly recovered.

A 45-year-old college professor of superior intelligence had an acute onset of a toxic psychosis with auditory and visual hallucinations, delirium, abdominal

pain, and orange-colored urine. The urine examination was strongly positive for porphyrins. He was given 100 mg. Frenquel intravenously, and two hours later was much improved. The next day he relapsed. Within four hours after receiving 50 mg. Frenquel intravenously and 50 mg. orally, he was symptom free. He was placed on Frenquel, 100 mg. t.i.d., and two days later was discharged from the hospital fully recovered.

Frenquel was of no value in the treatment of the neurotic patients in this study.

Although no rigid controls were maintained to validate this observation it should be mentioned that Frenquel combined with electroconvulsive therapy may be advantageous. A sufficient number of patients who received combined Frenquel-electroconvulsive therapy appeared to respond more favorably and with fewer treatments than normally expected.

Conclusions

Frenquel is an interesting drug. The results obtained with it in the treatment of acute psychotic states are variable and inconsistent. Nevertheless, the findings in this study suggest that it should be tried in acute schizophrenic reactions, particularly in those of recent origin in which the symptoms resemble those of mescaline and LSD-25 psychoses. It also may benefit senile confusional states, especially those originating after surgery. Although the results obtained in toxic psychoses are difficult to define, the use of Frenquel in such states is recommended. Finally, the combination of this drug with electroconvulsive therapy should be investigated further.

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THE PHANTOM LIMB: A PROPOSED THEORY OF UNCONSCIOUS ORIGINS

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The centralist and peripheralist theories about the origin of the phantom limb phenomenon have some rather definite limitations. The centralist theory, elaborated by such individuals as Pick (5), Head (2) and Schilder (7), claims that there are processes in the central nervous system which are more or less independent of sensory stimulation from the periphery and which perceptualize the various body organs. In other words, a "body image" is acquired by the central nervous system through learning and physical maturation. Schilder felt that the phantom "... is the reactivation of a given perceptive pattern" (p. 67). However, he recognized the essential limitations of all existing explanations of the phantom when he said: "In general, the amputated limb appears shrunken and closer to the body than the other. To some, the amputated hand appears as a child's hand right at the shoulder. We have no explanation of these interesting phenomena" (8, p. 94).

The limitation of both centralist and peripheralist conceptions is precisely that they do not resolve the many subphenomena associated with the phantom. The proponents of the peripheralist theory claim that the phantom is a product of nervous sensations arising from the stump; in other words, that it is a projection of sensations to areas supplied by nerve trunks. However, they fail to explain the persistence of phantoms after various kinds of corrective surgery on the stump area or the modifications of sensation when different stimuli are applied to the stump. Again, the limitation of this view is the lack of a suitable explanation for the subphenomena associated with the existence and persistence of the phantom over periods of time.

More recently, motivational and emotional factors have been emphasized by analytically-oriented investigators. The phantom has been thought of as representing a narcissistic desire to maintain the body's integrity in the face of a realistic loss or a rejection of symbolic castration of a body organ. Kolb, Frank and Watson (4) have stressed emotional components: "The attitudes of the mother and the father leave an indelible impression on that child as far as his later concept of himself as a person is concerned. Pain is often intermittent and represents an emotional response (which is) an indication by the patient that he is suffering from the loss of an important part which has significance in terms of his relationships with others. In certain patients these symptoms of pain could be induced by reference to some known cause of anxiety in the patient's interpersonal life." The success of the psychotherapeutic approach where other methods of treatment have failed lends weight to the idea that unconscious motivational and emotional factors are implicated in the production of the phantom after amputation or paralysis. While this approach still does not explain the dynamics of the phantom, it indicates that more attention should be given to the elaboration of unconscious factors in the development of phantoms, painful and otherwise. A valuable piece of insight has been offered by Rosner (6), who says about the phantom: "Such phenomena occur in apparent conformity to forces that are beyond the influence of the conscious will of the patient. But the phantom limb is not altogether beyond control. It can be influenced, according to Betlheim, by hypnosis, by suggestion or other psychological mechanisms. Its behavior is not altogether capricious and unpredictable but conforms to the laws of the unconscious as described by Freud" (p. 162).

A reassertion of and amendment to Rosner's statement is proposed: that the phantom *is* a product of the unconscious (which presumes a neurological substructure); and, in addition, that the laws of the unconscious which control the phenomenon *parallel Freud's theory of four factors involved in the production of dreams—those factors which he labelled the "dream work"*. Indeed, a tentative theory of the phantom

might legitimately develop along lines parallel to those set down by Freud in his explanation of the origin of dreams.

One major assumption of a parallel theory would be that the phantom—like the dream—is a product of unconscious wishes or desires. Freud (1) describes the process by which the wish acquires visual, auditory and tactile representation by postulating that during sleep the motor release of thought-impulses is restricted. These impulses are then deflected back through the psychic systems and acquire representation by means of this "regressive" process. The impulses, in their backward flow, reawaken the images that exist ordinarily in a latent, dormant state within the so-called "mem" (memory) systems. Representation in visual, and other imagery takes place within these "mem" systems. Essentially, it is through the operation of a regressive process that the wish-impulses are transformed into various perceptions during the sleeping state.

If we postulate that the motive power necessary to produce the phantom is an unconscious wish, how then is it possible for these wishes to acquire representation (i.e., to become experienced visually, tactually, etc.) during the waking life? Obviously, motility is in full sway during the waking life: must not motility cease in order to produce the regressive process? No! In the first place, Freud mentioned that in certain morbid states (e.g., hysteria and paranoia) the phenomenon of regression is clearly observed during the waking state. The hallucinations of such individuals are evidence of a regressive process in which suppressed memories from the unconscious are revivified under the motive power of certain wish-impulses. In the second place, a cessation of motility has actually occurred in the case of the phantom. In amputation, the missing limb is obviously no longer motile; and in paralysis of limbs, movement is impossible. A restriction of motility has occurred in these cases, and therefore the necessary pre-condition for the functioning of the regressive process is satisfied.

Are there other relationships between the phantom and dreams? Close observation reveals certain resemblances between the subphenomena associated with the phantom and the factors involved in the "dream work" (condensation, displacement and secondary elaboration). Freud considered these factors as distortions which occurred when it was necessary to censor certain wish-impulses. A censorship was recognized whenever a wish-fulfillment was disguised or made otherwise unrecognizable in the manifest dream; in this process, there must presumably be present a tendency to defend against the wish so that it could express itself only in some distorted fashion. Now in the case of a limb amputation it would seem reasonable to suppose that acting against the wish to use the lost limb is the wish to adjust to the reality of the loss. Since these wishes are rather grossly inconsistent (it should be recalled that inconsistent wishes can live quite comfortably side by side in the unconscious), a process resembling censorship might be presumed to enter in and promote distortions that are similar to those that Freud had in mind when he considered dream distortions.

In the present view, it seems reasonable to assume that the subphenomena which are associated with the phantom (such as telescoping and the dropping out of parts) may be best explained as distortions brought about by a certain kind of censorship of the original wish-impulses to use the lost or disabled limb. Telescoping, or the subphenomenon in which the phantom appears to approach the stump and disappear into it with time, would constitute one kind of distortion resulting from the censorship; the dropping out of parts of the phantom with time would constitute another (closely akin to Freud's factor of condensation of dreams in which certain parts of the dream-thoughts are omitted from representation).

It is not the purpose of this paper to explain the changes (or subphenomena) in the phantom in terms of Freud's four factors. It is a guess that whereas these changes are produced by factors which parallel those described by Freud, they are not identical with Freud's factors. Studies of the phantom should be directed at determining the specific character of unconscious factors which produce and cause changes in the phantom. Such studies could be of great value in helping to chart some areas of the unconscious which have remained obscure.

Generally speaking, the unconscious origin and the wish-fulfilling function of the phantom

can account for many of the facts supplied by investigations of the phantom to this date. Painful phantoms, for example, seem to be an exception, occurring in about 5 per cent of all amputations (figures vary between 2 per cent and 10 per cent). Under a theory of the unconscious origin of the phantom, the painful phantom might be produced by either of two conditions (or a combination of both): 1) nerve irritation at the stump which is of sufficient strength to provoke the unconscious wish to use the intact organ, and 2) psychic conflict between the unconscious wishes to use the intact organ and to adjust to the reality of having lost the organ. The painful phantom will be considered again later in this discussion.

A theory of the unconscious origin of the phantom could account for the case in which the phantom appears to penetrate a solid object placed before it by positing the existence a factor similar to Freud's secondary elaboration. Indeed, this interesting subphenomenon seems to provide weight for the argument that the phantom is an unconscious wish-fulfillment. As the product of an unconscious wish the phantom could not possibly "adapt iself" to an object held in front of it, for example, by bending because the image projected is in the nature of an hallucination. When individuals report that the phantom has "gone right through" a solid object, it would appear that they do so on purely logical grounds. How other than by a desire for intelligibility (or what the Gestaltists call "good fit") could one explain why an amputee reports that his phantom has penetrated a solid object?

Absence of phantoms has been reported in children amputated at the ages of 3 to 5 years. These cases would suggest that a fund of experience is necessary for the development of the phantom (i.e., a fund of wishes revolving about individual body organs). Though phantoms of the facial parts, breast and penis have been noted, their frequency is much less than limb phantoms. This fact would tend to be consistent with the idea that some impairment in mobility must exist as a pre-condition to the production of the phantom. The face, breast and penis (being less motile than the limbs) would probably not so easily satisfy the necessary pre-condition.

Many other subphenomena associated with the phantom have been reported in the literature. Generally speaking, these would seem to be more admissible to explanation on the theory of an unconscious rather than a central or peripheral origination. A neurological substructure of the subphenomena cannot, of course, be denied; but a neurological theory is no more sufficient to explain their existence than it is capable of explaining the process of thinking. Neither a central nor peripheral theory can rationally account for the beneficial results of psychotherapy on painful phantoms; a theory of unconscious origin is more consistent in this respect. On the other hand, a theory of unconscious origins is not inconsistent with successful treatment of the phantom by operations on the stump for removal of scar tissue, etc., or operations on sympathetic ganglia. In these cases reduction in nerve irritation would lessen chances of arousing wish-impulses revolving about the lost limb.

Assuming that pain originates either independently (i.e., by nerve irritation) or as an integral part of the wish-impulses, more than one method of treatment would be employed in dealing with painful phantoms. The method most likely to meet with success, of course, would be a psychotherapeutic (if not psychoanalytic) approach which delved into unconscious material, such as has been described by Kolb (3); yet there would certainly be instances of painful phantoms which would succumb to nothing other than a surgical treatment of nerve irritations. In all cases, however, reason would dictate that the psychotherapeutic method should be tried before the surgical in alleviating pain.

Due probably to the fact that somatic pain has attended the phantom in a certain percentage of cases, its investigation as a normal psychobiological phenomenon has not received much emphasis. In a recent article, Simmel (9) makes the statement that ". . . I cannot think of any other phenomenon, any other set of facts, from which one can tease out quite as elegantly the separate contributions of basic anatomy and physiology; of normal learning in the course of development of the individual of special motivational components, that is,

the psychiatric problems, and of the influence of certain social and cultural factors" (p. 638). In this paper an effort has been made to fit the multiform and multilevel factors that enter into the production of the phantom within a single inclusive theoretical matrix. A theory of an unconscious origin of the phantom would be more able to integrate the many apparently inconsistent facts that have surrounded and obscured the phenomenon than either a centralist or peripheralist view. This paper attempts to draw a certain parallel (but not an identity) between the dynamics of the phantom and the dynamics of the dream described by Freud. Both are viewed as products of the unconscious; both as regressive phenomena; both requiring as a necessary precondition certain restrictions on motility. It is hoped that future investigations of the phantom will furnish experimental documentation and support for this theoretical framework.

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RELIGIOUS BACKGROUND OF PATIENTS IN A MENTAL HYGIENE SETTING[1]

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The incidence of mental disorders within various religious groups is of considerable interest, among other reasons, because religion, directly or indirectly, may often be significantly related to the psychodynamics of the disorder. Most of the investigations concerned with this problem have dealt with hospital patients (3, 6) although there has been some recent effort to study populations outside of a mental hospital setting (2, 5).

Apart from the question of the distribution of emotional disorders in religious groups there is a related and highly meaningful (albeit relatively overlooked) problem of the representativeness of such groups in treatment facilities. Are these groups proportionately representative of the community from which they come, and if not, what influences operate to produce such disproportionate representations?

Among the characteristics studied in a recent survey (1) of various sociological, cultural, and psychopathological characteristics of patients in individual psychotherapy at the Mental Hygiene Treatment Group of the Psychiatry and Neurology Unit, Veterans Administration, New York Regional Office,[2] was that of religious background of patients (defined in terms of parental religious faith). Information was gathered on a total of 339 patients in individual treatment during the summer of 1953, representing approximately 90 per cent of all such patients.

The distribution of religious backgrounds is revealed in table 1. It will be seen that slightly over one-half of the group are of Jewish background, close to three-tenths Catholic, and approximately one-eighth Protestants.[3] In the geographic area served by the clinic the religious background of the population approximates 45 per cent Roman Catholics, 25 per cent Jews, 25 per cent Protestants, and 5 per cent others.[4]

On the assumption that the local distribution is representative of the religious background of the veterans in this area, the incidence of Jewish patients at the clinic is twice their proportionate number in the population, Protestant patients one-half their number, and Catholic patients two-thirds their number. The chi-square test of statistical significance indicates the clinic distribution to be significantly different from the expected one at beyond the .001 level of confidence (chi-square of 134 for 2 degrees of freedom).

How can this markedly disproportionate representation be accounted for? Is it a reflection of the prevailing incidence of psychopathology in the three populations, of their receptiveness to psychotherapy, or a combination of these and other factors? Does it involve the variable of religion at all? These questions are, quite obviously, difficult to answer definitively. One important reason, among others, is the absence of reliable information as to the actual incidence of psychological disturbances in each group residing in this area. Nevertheless, some attempts to clarify the problem can be made.

One consideration that comes immediately to mind is whether the clinic distribution of religious backgrounds is related to the *severity* of emotional disturbance (e.g., since the Jewish group predominates in the clinic, does it also manifest a proportionately greater incidence of psychosis than the other groups?). In order to determine whether such a relationship exists, the three religious groups were compared for the incidence of neurotic and psychotic diag-

[1] From the New York Regional Office of the Veterans Administration.

[2] Hereinafter referred to as "clinic".

[3] With Negro patients eliminated, the clinic breakdown is: Jews 54 per cent, Catholics 29.8 per cent, Protestants 10.3 per cent, others and unknown 5.9 per cent.

[4] According to statistics compiled from the following sources: American Jewish Congress, the Protestant Council of the City of New York, and the New York Public Library; the Health Insurance Plan of Greater New York in a recent survey arrived at a similar distribution (cf. *The New York Times*, March 21, 1955, page 19).

TABLE 1.—DISTRIBUTION OF RELIGIOUS BACKGROUND

Religion	No.	Per Cent
Jewish	172	50.7
Catholic	100	29.4
Protestant	43	12.6
Other	7	2.3
No Information	17	5.0
Total	339	100.0

noses. Table 2 reveals the results of this comparison.[5] There were no statistically significant differences in the frequency of psychotic or neurotic diagnoses among the three groups (chi-square of 1.12 for 2 degrees of freedom). Each group comprised approximately one-third psychotic and two-thirds neurotic patients.

The possibility that the three groups are of different educational levels and that the different representations are a resultant of this variable rather than religion was considered. Thus, people who have attained a high educational level may be more aware of psychotherapy as a method of treatment than those who have limited schooling. To compare the educational level for the groups, the median number of years of schooling for each group was computed. There were no significant differences in medians; all approximated the level equivalent to completion of high school. The median educational achievement for the Jewish group was 12.23 years, for the Catholic group 11.82 years, and for the Protestant group 12.13 years.

Another possibility for the skewed religious representation is the operation of the factor of acculturation. Does the distribution shown in table 1 reflect generation in the United States rather than religion? Table 3 indicates the relationship between generation in the U. S. and religious affiliation of the patients. Patients whose parents were born abroad occur predominantly in the Jewish and Catholic groups (52 per cent and 66 per cent, respectively). The bulk (65 per cent) of the patients of Protestant background, however, are at least second generation Americans. The representation according to religious background thus reflects, to some degree, the factor of acculturation. Obviously, however, there is not a one-to-one relationship between these variables since patients of Jewish background are most numerous in the group under survey although patients of Catholic background show a greater percentage of first generation native Americans.

Still another variable that should be considered is that of socio-economic status. Is the skewed religious distribution a reflection of socio-economic status (4)? Since the survey questionnaire was not designed to measure socio-economic status directly, a rough index, patient's employment status, was used in considering the influence of this variable. Table 4 shows the relationship between religious background and employment status. Taking the extreme groups in terms of clinic representation, the patients of Jewish background show the smallest percentage (13.8 per cent) of unemployed and/or laborers compared with those of Protestant background (41.8 per cent). Considering the category of professional employment, the Jewish group shows the highest proportion (19.1 per cent), the Protestant group is next highest (16.2 per cent), while the Catholic group is lowest (12 per cent). The data, thus, suggest that the religious representation in the clinic is, to some degree, reflecting the socio-economic status of the patients.

Cultural and traditional factors closely related to the various religious backgrounds, undoubtedly, also play significant roles. Thus, the high premium which Jewish people place on mental activities, their enlightened attitude toward emotional derangement, their predilection for introspection, and the relative lack of conflict between their religious doctrine and psychoanalytic therapy (in contrast to the partial opposition expressed by the Catholic Church) are quite probably involved in the high Jewish patient representation. A factor in the marked under-representation of the Protestant group may well be the strongly ingrained cultural (partly Calvinistic) view in America that one must work out one's own salvation, one should be independent and have no need (and *ought not* to have need) for any one else to tell one what to do or how to live.

Such considerations indicate that the distribution according to religious background involves, in fact, a number of other variables

[5] This table does not include those cases (31) where patient's religious background was other than the three major religious denominations, where information as to religion was unavailable, or where diagnosis was primarily neurological.

TABLE 2.—Religious Background and Diagnosis

Diagnosis	Jewish		Catholic		Protestant	
	No.	%	No.	%	No.	%
Psychosis	58	34.3	36	37.5	15	35.0
Neurosis	111	65.7	60	62.5	28	65.0
Total	169	100.0	96	100.0	43	100.0

Table 3.—Generation in U. S. and Religious Background

Generation	Jewish		Catholic		Protestant		Other		No Information	
	No.	%	No.	%	No.	%	No.	%	No.	%
1st generation	89	51.7	66	66.0	14	32.5	7	100.0	1	5.9
2nd or more generation	69	40.1	32	32.0	28	65.1	0	0	10	58.8
No information	14	8.2	2	2.0	1	2.4	0	0	6	35.3
Total	172	100.0	100	100.0	43	100.0	7	100.0	17	100.0

TABLE 4.—Religious Background and Employment

Job	Jewish		Catholic		Protestant		Other		No Information	
	No.	%	No.	%	No.	%	No.	%	No.	%
Unemployed	17	9.8	20	20.0	12	27.9	1	14.3	4	23.5
Student	7	4.0	11	11.0	5	11.8	1	14.3	2	12.0
Post Office	20	11.6	5	5.0	2	4.7	1	14.3	1	5.8
Laborer	7	4.0	14	14.0	6	13.9	1	14.3	5	29.4
Professional	33	19.1	12	12.0	7	16.2	0	0	1	5.8
Salesman	26	15.1	5	5.0	2	4.7	0	0	0	0
Other	56	32.5	30	30.0	6	13.9	3	42.8	4	23.5
No information	6	3.9	3	3.0	3	6.9	0	0	0	0
Total	172	100.0	100	100.0	43	100.0	7	100.0	17	100.0

including acculturation, socio-economic level and cultural factors. In addition to the variables directly concerning the patient, the attitude and background variables of the screening or intake doctor, as well as the psychotherapist, may be important factors influencing the religious representation. These will be investigated in another study. In the absence of definitive information as to the actual prevalence of mental disorder in the three major religious denominations, it should also be noted that the possibility cannot be excluded that the clinic representation of religious backgrounds of these patients reflects the incidence of comparable psychopathology in each respective group in the community. Roberts and Meyers (5) report that in a survey made of the New Haven population under psychiatric treatment, the incidence of psychoneurotic disorders among Jews was two and a half times expectation. Here, again, this may be a matter of greater amenability to treatment for this group. The latter problem, as well as a study of the attitudes of the three religious groups (perhaps refined as to those practicing and not practicing their faith) toward psychotherapy, is significant enough to warrant further investigations.

Summary

This investigation was concerned with the representativeness of the three major religious backgrounds of a random sample of 339 patients receiving individual psychotherapy at the clinic of the Mental Hygiene Treatment Group, Psychiatry and Neurology Unit,

Veterans Administration, New York Regional Office, during the summer of 1953. It was found that the clinic distribution of religious backgrounds was significantly at variance from that expected on the basis of the actual distribution of religious backgrounds for the population residing in the New York area served by the clinic.

The incidence of Jewish patients at the clinic was twice their proportionate number in the population, Protestant patients one-half their number, and Catholic patients two-thirds their number. An analysis of possible reasons for this distorted representation suggested the influence of a number of other variables including acculturation, socio-economic status as well as related cultural factors. In the absence of information as to the actual prevalence of mental disorder in the three major religious denominations population-wise, the possibility could not be excluded that the clinic representation reflected the incidence of comparable psychopathology in each respective group in the community. Further investigation of the latter problem as well as of the attitudes of the three religious groups toward psychotherapy is needed.

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NORMAL AND NEUROTIC OLFACTORY BEHAVIOR IN MONKEYS

A Motion Picture[1]

JULES H. MASSERMAN, M.D., AND CURTIS PECHTEL, PH.D.

The film first illustrates an apparatus in which experimental animals may be trained to respond to controlled auditory, visual and pure or combined olfactory stimuli (fig. 1). Eighteen monkeys (10 rhesus, 5 American spiders, 2 vervets and 1 mangabey) when permitted to show spontaneous olfactory preferences, were generally drawn to substances with fruity aromas, but showed no aversions to food even when it smelled of indol or skunk. Odors infused into the apparatus for from 15–60 sec. proved to be less effective than sound or light signals as cues for the animals to operate switches for food rewards; however, after from 5 to 12 weeks of special training, such olfactory conditioning could be established.

Induction of Experimental Neuroses

After several months of such observation and training, each monkey was subjected to the sudden appearance of a small rubber "snake" in the food box at the moment of conditional food-taking. From 12 to 15 of these conflictful experiences, each associated with the smell of lemon, pine needles or anise, resulted in the induction of a severe and protracted experimental neurosis variously characterized by inhibitions of normal feeding, play and exploratory activities, hypersensitivity to all stimuli, frequent and violent startle and aversive reactions, serious neuromuscular and organic dysfunctions, deviated erotic behavior, evidences of hallucinatory and delusional experiences, and persistent alterations in interanimal relationships parallel to those that occur in human neuroses and psychoses (1, 2, 3, 4). In addition, the monkeys also developed intense olfactory phobias which quickly generalized from the fruity odors specifically associated with their neurotigenic conflicts to all other olfactory stimuli. Conversely, as the experimental neurosis was mitigated by various methods of individual or group therapy, these olfactory generalizations were reversed: i.e., previously neutral odors became progressively better tolerated, whereas fruity aromas continued to evoke minor aversive responses even after nearly all other evidences of neurotic behavior had disappeared.

Effects of Deodorants

Of the many deodorants tested, only one, a chlorophyll compound, markedly alleviated or prevented olfactory reactions in experimentially sensitized monkeys; however, its mode of action was not determined.

Summary

Odors are well tolerated by normal monkeys and are less effective than signals in other modalities as cues for learned behavior. However, when the animals are made experimentally neurotic, aversive responses to all olfactory stimuli are markedly increased. During recovery, these aversive effects can be significantly diminished by a deodorant, but olfactory stimuli directly or indirectly associated with the original neurotigenic conflict remain phobigenic longest.

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[1] Presented before the annual meeting of the Society of Biological Psychiatry, Chicago, Illinois, April 27–28, 1956. The film is 16 mm., black and white, silent, with a running time of about 15 minutes.

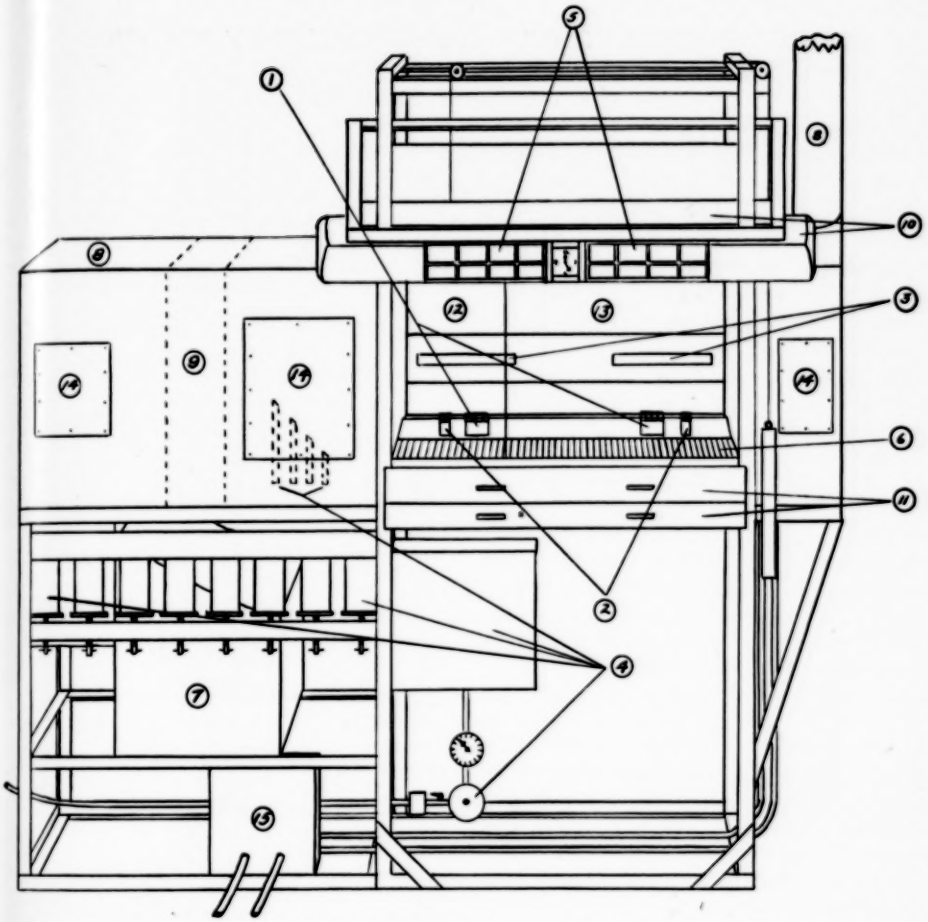

FIG. 1. An apparatus for the study of olfactory reactions in normal and in experimentally neurotic cats and monkeys.

Key to diagram of experimental apparatus:

1. Food boxes with hinged lids which receive rewards from automatic feeding system. (Conflicts engendered here by presentation of rubber snake or air blast stimuli.)
2. Pedals to be manipulated by the animal to activate feeding signals.
3. Visual configuration stimuli.
4. Apparatus for administering olfactory stimuli, including solenoid valves and air gage.
5. Panel for photographic signals.
6. Grill floor which can be electrified.
7. Blower for olfactory stimuli.
8. Air stream chamber.
9. Carbon filtration bank.
10. Photographic and illuminating light banks.
11. Grill and cleaning drawers.
12. Glass door.
13. Observation panel.
14. Access panels.
15. Electrical switch box.

CAROTID SINUS CONVULSIONS TREATED BY SURGERY

SAMUEL ROSNER, M.D., F.I.C.S.

A case of convulsions as a result of a "carotid sinus sensitivity" will be described. Weiss and Baker in 1933 (6) and Ferris, Capps and Weiss in 1935 and 1937 (3, 4) discussed the carotid sinus and its relation to syncope and convulsions. In the latter paper they described three types of attacks: 1) Unconsciousness due to cerebral anoxemia as a result of cardiac asystole. 2) Attacks due to cerebral anoxemia caused by fall in blood pressure. 3) Unconsciousness without any marked change in blood pressure or heart rate.

The first two types listed above are to my mind due to one basic cause and vary only in degree. Brain (1) gives as causes of carotid sinus dysfunction, scarring of tuberculous adenitis, atheroma of the artery, and rarely tumor. As general causes he lists menopause and dietary deficiency associated with chronic alcoholism.

Various investigators have entertained the idea of the carotid sinus having a possible affect in epileptic seizures. Danielopolu and Marcu (2) felt that section of all the fibers of the carotid sinus and cardioaortic nerves may possibly abolish epileptic seizures in some cases. This would be physiologically a hazardous procedure since Greiwe (5) showed that in animal experiments such a procedure resulted in death within 24 hours.

The carotid sinus will cause a reflex fall of blood pressure and a slowing of the pulse if the pressure within the sinus is raised; and vice versa. These reflex changes are governed by the sinus nerve of Hering, a branch of the glossopharyngeal nerve and the medullary vasomotor centers.

Case History

P. S., a white male, age 41 years. Patient referred by Dr. S. Warman. In March, 1955, the patient went down to get the papers at night. He felt dizzy and lost consciousness. There was no incontinence of urine or feces. In Sept., 1955, there was a burning dry sensation in the throat followed by loss of consciousness. The third attack came in Oct., 1955, while shaving. His wife heard him fall. She found him lying, "stiff with his mouth open."

The patient worked as a manager of a super-market and had been a healthy but nervous individual all his life. Since his stay in the army, 1944, he had suffered from "chills", once or twice each year, which were relieved by taking a drink of Scotch whisky and going to bed.

The day following an attack, 10/12/55, the neurological findings were as follows:

B.P. 130/80, P.R. 78 per min., congestion of both optic discs, absent abdominal reflexes in both lower quadrants and positive Babinski sign, bilaterally. Dilantin and Serpasil were prescribed.

Skull x-rays were negative except for hypervascularity in the frontal region.

Eye consultation showed no constriction of visual fields and no papilledema.

Fasting blood sugar was within normal limits.

Electroencephalogram was read as normal for a tense individual.

In March, 1956, the patient was admitted to hospital because of frequently recurring attacks of unconsciousness followed by an epileptic attack which was tonic, then clonic. The tonic portion lasted about 1½ minutes and the clonic portion about ½ minute. The attacks came about every half hour. The patient was calm between attacks and volunteered the information that each attack began with a "sensation" in the right side of the throat. Injections of sodium luminal increased the frequency and the violence of the fits. During an attack the B.P. fell to 70/40 and the pulse rate ranged between 40 and 50 per min.

Pressure over either carotid sinus brought on an attack. Local injection of novocaine in the region of the right carotid sinus stopped the attacks for six hours. Repeated injection of novocaine but with addition of 2 cc. of injectable Benadryl stopped the attacks for 12 hours.

A Cardiologist was called in to confirm the diagnosis of carotid sinus epilepsy. He stimulated the carotid sinus and got a typical fall in blood pressure and bradycardia. The electrocardiograph here shown were taken at the time of a fit.

I decided to do a stripping of the right carotid sinus because the "aura" was on that side and because local block stopped the fits temporarily. This was carried out the next day. No gross pathology could be seen at the side of operation. After operation, the blood pressure went up to 130/80 and the pulse rate to 80 per min. These have not varied from normal limits. The patient has remained well except for a momentary weak feeling on a very hot July day. At the last examination in Sept., 1956, the B.P. was 130/80, pulse rate was 80 per min., and the patient was perfectly well and doing his usual work.

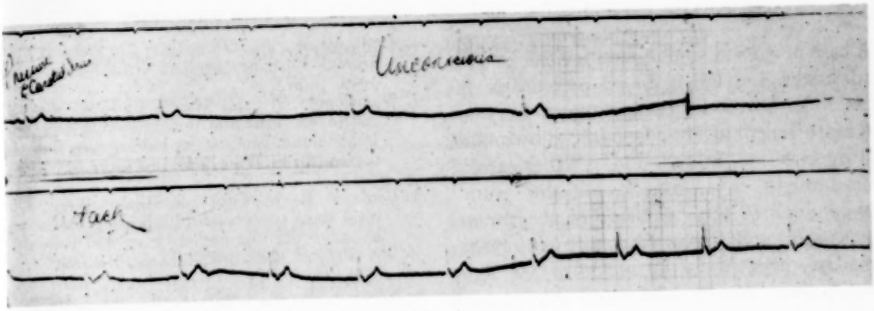

FIG. 1

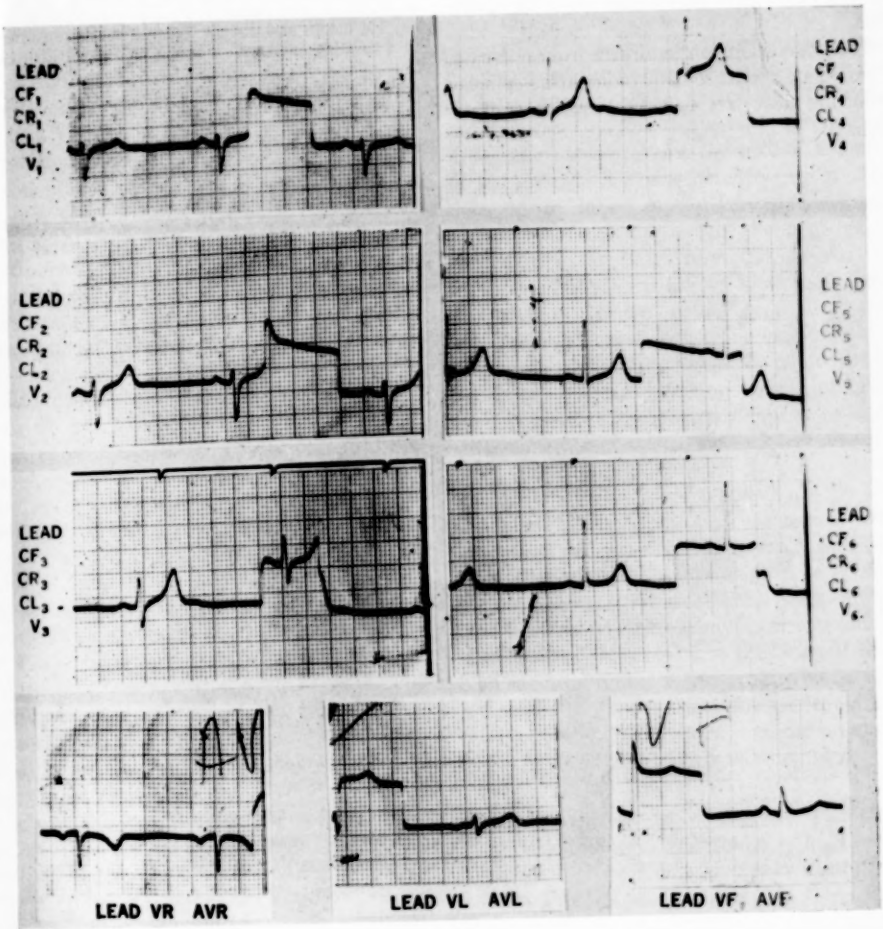
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FIG. 2

Summary and Conclusions

A case of carotid sinus epileptic attacks with bradycardia and fall in blood pressure is described. The attacks became more frequent and more violent after phenobarbital by mouth and by injection. Stimulation of either carotid sinus brought on an attack, but the "aura" was confined to the right side of the throat. Novocaine, and novocaine with injectable Benadryl, injected in the region of the right carotid sinus greatly prolonged the interval between the attacks. Stripping of the carotid sinus on the side of the "aura", the right side, has resulted in a beneficial result, no attack having recurred in six months since the operation.

If a conclusion can be drawn from one case, I would state that so-called idiopathic epilepsy is for the most part a cerebrovascular dysfunction.

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BOOK NOTES AND REVIEWS

Books received are acknowledged and given a brief description in this section. Selections serving a variety of interests will be made from these for a more extensive review, as far as space will allow.

BOOK NOTES

Faust, Clemens. DIE ZEREBRALEN HERDSTORUNGEN BEI HINTERHAUPTSVERLETZUNGEN UND IHRE BEURTEILUNG. [Stuttgart: Georg Thieme Verlag, 1955. Pp. viii + 111. $3.50.]

"The Focal Brain Lesions in Injuries of the Occipital Lobes and their Evaluation" is a monograph by a "Dozent" of the University at Freiburg. The G. Thieme's publishing firm's representative in this country is the Intercontinental Medical Book Corporation in New York. The author began his medical career and scientific investigations under the direction of K. Kleist. He has been interested in optic agnosia for a great many years, and reports, in this well documented book, his experiences, examination methods, and results of investigations, the main purpose of which has been a more accurate and more objective measurement and evaluation of optic agnosia, especially of the milder and frequently overlooked degrees of optic agnosia. In separate chapters he deals with misrecognition or agnosia of objects, faces, writing and printing, colors, etc. The study is based on a large number of cases which were carefully examined with clinical, psychological, laboratory, and other methods. The conclusions are a result of team work; psychologists, ophthalmologists, otologists, pathologists as well as neurosurgeons contributed their opinions. One of this monograph's contribution is adding evidence to the view that some cases of clinically pure schizophrenia suffer from cerebral tumors. One man manifested a left-side depersonalization symptom; autopsy revealed a large right parietal-occipital tumor.

The monograph contains many case studies in addition to generalizations. There are samples of psychological tests (new variants), photographs of visual fields, pneumoencephalograms, and brain sections, as well as clinical information. This contribution will be of real interest to all who are interested in a more accurate and more objective evaluation of actual sensory-intellectual defects contingent upon occipital focal tumors. Publications of this kind are rather rare.

Steiner, Franz. TABOO. [New York: Philosophical Library, 1956. Pp. 154. $4.75.]

In the preface, Evans-Pritchard, professor of social anthropology at Oxford, gives a brief biography of the author who died at the age of forty-three in 1952 as lecturer in social anthropology in the University of Oxford. This little book contains the text of a course of lectures which Steiner was to deliver. The question of taboo was discussed by many authors, notably by Freud. Steiner's main contributions are two. First, he clarifies the meaning of the term taboo, what it includes and what it excludes, pointing out the inconsistencies and other logical inadequacies of a number of definitions available in literature. Secondly, he cites anthropological observations in a rather thorough attempt at showing what taboo is in actual life and how the different definitions and theories of taboo fit the facts. His scrutiny is close and thorough. The result is that most theories are found to be invalid. The reasoning is precise and the knowledge of facts is impressive. The book is weak on the positive side of the question: the author does not reach any positive conclusions himself. However his discussion is on a high level of thought and erudition. Anyone interested in taboo will want to study this book carefully. Laura Bohannan did an excellent job of editing Steiner's lecture notes.

Klein, D. B. MENTAL HYGIENE: A SURVEY OF PERSONALITY DISORDERS AND MENTAL HEALTH. [New York: Henry Holt and Co., 1956. Pp. 654. $6.75.]

This revised edition has the same general plan as the first: a general introduction in

which the nature and scope of mental hygiene and its historical background are outlined, a section on the nature of mental disorders, a section on prophylaxis of mental disorders, and a final section on promoting mental health. The author suggests that uninitiated readers might prefer to read the two technical middle sections last.

In the new edition the author, who is Professor of Psychology at the University of Southern California, has expanded the beginning orientation to include more historical data as well as outlining mental hygiene problems. The author presents a telling appraisal of the shortcomings of the mental hygiene movement which has been in existence for almost fifty years, covering such realistic reasons as inadequate budgetary appropriations by our legislatures.

The book presents a well-rounded approach to the subject, stressing the multi-disciplinary background of mental hygiene in the biological and social sciences, various fields of psychology and ethico-religious values.

The range of experimental material covered is tremendous: from early reforms of Pinel to the recent Schizophrenic Pilot Project of Stockton State Hospital. The author should be complimented on his excellent choice of quotations from different points of view, such as Boisen.

This book should be commended for not offering itself as a panacea for personal maladjustments. Individuals desiring this are referred to the proper source—psychiatric clinics and the like. Instead, the book offers an educational course based on a scientific approach.

BOOK REVIEWS

Nacht, S. Ed.: La Psychanalyse d'Aujourd'hui [Paris: Presses Univ. de France, 1956. Pp. viii + 869. ca. $8.00.]

Twenty-three authors, under the direction of S. Nacht, contributed to this French work on "Psychoanalysis Today". It appeared under the auspices of the Parisian Institute of Psychoanalysis. In his preface, Ernest Jones reminds us that active interest in psychoanalysis in France has never been widespread but was shown as early as 1905 by an essayist and writer of great renown, Romain Rolland. Beside him there was, before the first World War, a small number of men, among them Hasnard and Pitres. France has shown little response to analysis. One might wonder to what extent this is due to the vast French literature dealing quite intensively with the psychosexual problems of individuals. Another delaying factor may be the unwillingness of the French scientists to create "schools of thought". It seems impossible to acquire adequate skill in theoretical and practical psychoanalysis without prolonged and supervised schooling, which cannot be provided unless there is a group of teachers who agree on a body of concepts and methodological procedures. Jones indicates that the French analytic movement has now reached a higher level of stability than ever before.

The orientation of "Psychoanalysis Today" is strictly Freudian. Dissenters are mentioned briefly and their ideas are rejected in a few sentences. The only freedom of disagreement allowed in the text consists of elaborations on Freud's ideas and an expression of preference for one rather than another of Freud's formulations if several incompatible ones from different developmental stages of Freud's thinking are available. Throughout the book there is a keen awareness of the gradual changes brought about by the accumulated experience of decades. It is a good textbook, dealing systematically and exhaustively with all theoretical and practical problems of the psychoanalysis of children as well as of adults —normal, neurotic and psychotic. A great deal of coordinating and editing must have been required to create a work which gives the reader the fundamentals and the advanced material in an unhurried, clear and consistent manner despite the large number of contributors. "La Psychanalyse d'Aujourd'hui" appeared in two volumes but has a continuous pagination. The book will be of real value to anyone engaged in the teaching of analysis and as a reference book. An index would facilitate its use.

Z. A. P.

Hill, Lewis B.: PSYCHOTHERAPEUTIC INTERVENTION IN SCHIZOPHRENIA. [Chicago: University of Chicago Press, 1955. Pp. 216. $5.00.]

Dr. Hill has graciously and lucidly summarized the conceptions formed in a lifetime of therapeutic work with schizophrenics. After noting the behavioral manifestations of schizophrenia, the author attempts to render the impact of the illness in terms of the immediate and often awesome experience of the patient. Both the astute clinical observations and the subjective experience of the disease are then related to the dynamics and genesis of the acute schizophrenic process. (Thus this volume offered a pleasant contrast to two psychiatric texts which I was recently perusing. There one received the impression that the writers had spent a frustrating career with individuals whom they neither liked nor understood. Their texts largely consisted of personality descriptions with much overlap of the belittling adjectives between the different diagnostic groups.) Hill's suggestions for psychotherapy with schizophrenics are built upon the earlier analysis.

The author delineates the basic steps in the early psychological growth of the normal individual. These steps share in common the individual's withdrawal of "selfhood" from something which thereafter is assessed as external to himself. The infant initially feels everything to be within; he has no awareness of an outside world. The first step is the emergence from the mother-child unity of an ego which is preoccupied with survival and the comfort which signifies security. In establishing this distinction the baby learns to sort out its experiences which correspond to external events from those which are intrapsychic operations with symbols. The second step is begun by the infant's splitting of the maternal image into good and bad in order to obtain relief from the confusion created by the complexly functioning mother. A corresponding split of the self-percept ensues. The conscious self, i.e., ego, then ejects and denies that part of the self, called by Hill the id, which continues to maintain the intense attachment to the mother. The id has indefinite boundaries which embody part objects, i.e., an internalized maternal breast. The third step is the separation between the self and that part of itself which includes the animistic, savagely punitive image of the mother—the superego.

The interpersonal situation of the child who will become prone to schizophrenia compels him to falter at these crucial developmental steps. The immature mother of the schizophrenic ambivalently overprotects and rejects. Her hysterical and obsessive difficulties prevent her awareness of the reality of the child; she regards him as her toy or plaything. The child, supersensitive to the dangerous hostility of the mother, and assuming that she could omnipotently gratify all the yearnings of his infantile ego if only she chose to do so, appeases her by acting out her unrealistic fantasies.

Thus the schizophrenic-prone child fails adequately to distinguish himself from his mother. He thereby sets the stage for a chronic resort to futile magic in his efforts to deal with her. Presumably his more drastic splitting techniques as well as his greater cathexis of the maternal breast lead to large amounts of energy remaining in the id. The excessively strong id threatens eruption into the correspondingly defective ego. Modelled in large measure upon the real qualities of the depriving and punishing mother, the powerful superego further menaces the integrity of the ego. Expressions of aggression and mature sexuality are equally forbidden by the superego. The schizophrenic break is triggered by the temptation of a desired relationship to someone. The ego cracks under the destructiveness of the jealous maternal imago, i.e., the superego, and the primitive nature of the id cravings directed at the other.

A reader often senses an author's need to write out a problem so as to mould it into a definitive shape for himself, or to present a theoretical discussion and/or research results to help move forward the current boundaries of the science, and/or to gratify narcissistic or expulsive needs, etc. Here the reader is impressed by the generousness and helpfulness of the author in making available his extensive and carefully culled knowledge of schizophrenia. Dr. Hill has apparently directed much of his comforting and authoritative discussion at the new psychiatric resident. Hill would not only aid the apprentice to think through his

conceptual bafflement but would also supply some guidance for the deeper personal problems activated by the contact with schizophrenics.

This kind of approach by an author has its disadvantages. Not only is there an undermining of the grateful reader's motivation to think critically, but the author too seems little tempted to work through a certain vagueness in his argument. Often I had the impression of, at best, a rough consistency rather than of clearly logical sequence in the content.

Thus, after mention of the induction of a split in the ego structure by the earlier splitting of the mother imago, we are told neither the nature of the two dissociated self-percepts nor which self-percept interacts with the good as opposed to the bad mother. Hill also remains hazy about the content of the self-in relation-to-mother theme which remains conscious. While Hill states that the concept of the omnipotent maternal figure or breast is relegated to the id, it is uncertain whether the bad depriving mother figure or maternal part object may instead—or in addition—be part of the id, or even whether the characteristic of omnipotence results from a split other than that along the good-bad dimension.

Since Hill defines as the id what is generally regarded as unconscious ego, or self, and includes in the id the percepts of objects towards which it strives, it is incumbent upon him to state what significance this somewhat deviant definition has. This he does not do. Once the id is seen as having object assessments as well as strivings, then the distinction between ego and id becomes one of depth of personality level and degree of awareness only. Further, thematic structures on any level, including that of the "id", may boast a significant other who may act as an agent that rebukes or rewards on the basis of moral criteria, i.e., a superego precipitate. At any rate Hill does not succeed in clarifying the interrelationship or distinction between mental institutions in his presentation.

Other omissions were of a different order of importance. Despite Hill's attempt to present the actual experience of precipitously succumbing to schizophrenia, there is strangely little material on the archaic fantasies of the ill-person. (Probably this inattention was designed to avoid arousing the novitiate's ardor for symbol-chasing at the cost of his patient's deteriorating reality.) The expert weaving back and forth between intrapsychic and interpersonal proceedings by the author whets the desire for a fuller exposition of his theoretical integration of these interrelated phenomena and the usually divergent theoretical approaches.

I may now be criticizing Dr. Hill for writing a book other than the one he chose to do. My justification is that each chapter of the book gives testimony to his unusual degree of competency; it is to be hoped, therefore, that he follows the present work with a more finely wrought treatise.

STANLEY ROSENMAN

Róheim, Geza: Edited by W. Muensterberger and S. H. Posinsky: MAGIC AND SCHIZOPHRENIA. [New York: International Universities Press, 1955. Pp. 230. $4.50.]

Its crude organization and hodgepodge style clearly stamp this book as unfinished. A reviewer must express regret at a death which not only cut down one of the most creative psychoanalysts in interdisciplinary areas, but also apparently prevented consummation of a promising study. At the same time there remains the irreverent thought that even if Róheim had lived, he would have evoked chiding for his customarily unmethodical presentation. (I believe it was Flügel in the 1930's who devoted a couple of pages in a review of a Róheim monograph simply to lecturing the author on the advantages of systematizing and of following established usage in writing reports.)

A reader suffers threefold by this disjointed approach. He struggles—often in vain—to follow the discussion. He is mortified at being so little considered by the author. And most important perhaps, an anxious foreboding is set off by the author's seemingly succumbing to the primary processes characterizing the primordial topic instead of his demonstrating an exemplary control by a rational ordering and conceptual refinement of the data.

The book consists of two loosely joined essays. Part I, "The Origin and Function of Magic", is largely a psychoanalytically oriented narration of the magic found in primitive tribes. Part II, "Fantasies and Dreams in

Schizophrenia", is the report of a frankly non-therapeutic contact with a hospitalized schizophrenic patient. Because many readers will be alienated by the manner of presentation and because the work nevertheless boasts many suggestive insights, I would like to attempt a brief restatement of the author's main points.

The anxieties accompanying each stage of development instigate their fantasied alleviation. The reassuring fantasy goes beyond hallucinatory gratification of the present need: the magic-laden fantasy precipitates a counterphobic sense of potential mastery over the situation. At this point the schizophrenic halts. For he essentially believes that he and the world have already engaged in mutually destructive acts of so horrendous a nature as to make the outcome irreversible. The schizophrenic's "imagination magic", a disguise of restitution for his relinquishment serves merely as a substitute for action.

The healthy individual by contrast, makes constructive use of his magical idea that the world outside is ruled by his wishes and that he can obtain what he desires simply by desiring it. This universal notion supplies the prerequisite springboard of optimism for all reality-oriented behavior. When again frustrated by the external world, the withdrawal of libido to the ego once more produces inflated assumptions of one's power. These narcissistic conceptions then function as underpinning for renewed assertiveness in the real world of objects.

Life's fundamental anxiety, one which provides a matrix for the experience of later traumas and frustrations, is generated by the sundering of the dual unity between mother and child. The child's separation anxiety leads to various magical essays at restoring the communion. The core idea of magic—that one's thoughts and feelings can change the universe—is an obvious denial of the disunity. A variant major resolution of separation anxiety is the incorporation of the other. The resulting introject functions, however, as a source of castigation. The archaic superego thus gives rise to a new set of anxieties. Magical, i.e. counterphobic, measures arise to ward off or deny the superego's accusation that we are bad and its injunction that we therefore should be inferior and inept.

Róheim contends that the pleasure in one's own body may be another initial response to object loss. (I would suggest, however, that even this defiant capacity to obtain solace from one's own body is often understood as mediated by the incorporation of various part objects, i.e., the fantasy that one's organs which generate well-being were assimilated from the external world.) The erotic zones do more than offer consolation at a time of object loss. At the various libidinal levels of development the erotogenic zones or qualities of the body in the fore are further employed as weapons in the countermove against the apprehensions brought about by that level's efforts at banishing the fundamental anxiety. For instance, to protect against bewitchment, the society may encourage eating the feces of an animal like the cat which represents the witch. Because the child is consuming the witch, this measure ensures that the witch can not swallow the child with her evil.

Schizophrenia is the necromantic psychosis *par excellence*. That is, schizophrenics frequently claim to be practicing magic or that they are influenced by the wizardry of others. Therefore study of schizophrenia promises further illumination of the psychology of magic. At the same time, the tentatively consolidated psychoanalytic insights into the black arts may make more understandable the schizophrenic disease process. From his summary of the literatures Róheim concludes that there are four basic types of conjectured witchery spun out by the schizophrenic: 1) He holds the power to make or restore things and to influence people with the magic powers emanating from within, 2) he is subject to sorcery by others which generally operates via his mouth, 3) he readily identifies with others or with objects, and 4) he is really two persons incompletely united.

The productions of Róheim's patient pointed to an oral trauma as the origin of his disease. The patient had reacted to the trauma with aggressive fantasies of devouring and destroying the mother's body. These body contents then became retaliatory introjects which gnawed at his food and caused the retributive ruin of his own body. Restitutive introjects were then created in a futile try at coping with the annihilative internal beings. A confusion

of symbol and object followed from the failure of his cathexis to move back from the vividly animated internalized objects to the environment. (In contrast, the normal individual will attempt to return to the object by way of the "inside" image of that object.) In appraising his disease, the patient sometimes attributed it to his early starvation; in self-punitive moments he blamed his own aggressive acts directed at his mother's body.

The incomplete nature of the book's content becomes painfully manifest at several points. First, Róheim ignores the archaic structures of cognition which accompany and make possible magical thinking. Next, Róheim tends too often to label a given magical system of thought as stemming from a given libidinal stage, or he will state that one element of a magical system represents, say, coital authority or castration. Using his own word magic he then dismisses an entire complex magical system as fully explained. It is also our impression that Róheim might have considerably strengthened his argument by establishing that the magical technques developed by a given society are uniquely derived from and designed to handle the particular despoilments to which its members are subject. Finally, the schizophrenic patient who was presented at length should have been dealt with as more than just a fantasy-producing object. The reader is told virtually nothing of the patient's past history, family situation, or socio-cultural characteristics, e.g., religious, ethnic, social class, and occupational background. One consequence is that the reader remains unacquainted with the important relationship between the real qualities of the patient's parental figures and the oppressive savagery of the parental images which made each successively hazarded resolution of the infantile trauma untenable.

Before concluding, I would acknowledge that this criticism of a posthumously published treatise is justified only insofar as it helps eventually to realize the aims of this extraordinary psychoanalyst and anthropologist.

STANLEY ROSENMAN

BOOKS RECEIVED FOR REVIEW

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NOTES AND NEWS

SCHOLARSHIPS FOR HUNGARIAN REFUGEES IN BIOLOGICAL SCIENCES

To enable Hungarian refugees with appropriate professional backgrounds to go to work as quickly as possible for American crippled children, the National Society for Crippled Children and Adults today announced a special scholarship program.

The project, approved by the Easter Seal Society's Executive Committee, and announced by Dean W. Roberts, M.D., executive director, is designed for recently admitted refugees who already have basic training in physical therapy, occupational therapy, speech therapy, or in fields of medicine related to rehabilitation of the crippled.

Dr. Roberts said: "Among the 21,500 Hungarian refugees admitted to the U. S., there is a significant number of skilled persons already trained in the rehabilitation field. The Easter Seal Society will seek from this new manpower pool college graduates and persons with technical training in the biological or medical sciences who are interested in further specialized training leading to helping our handicapped population."

He pointed out that the National Society plans to communicate with appropriate refugee organizations and outline the needs, opportunities and requirements in rehabilitation and to seek their help in locating and screening persons with the requisite interests and background. Evaluation of training needs will be made in terms of technical preparation by U.S. standards and the kind of training necessary for the person to become an acceptable worker.

"Types of scholarships that will be available will provide in-service training, refresher courses, short and long term university or technical school training," Dr. Roberts said. "We will seek the cooperation and participation of the various professional associations and appropriate training schools in this venture."

The scholarship program will be implemented as rapidly as possible, he said.

Dr. Roberts also announced that because of the concern of the Easter Seal societies nationwide for the plight of the Hungarian refugees in this country, facilities and services of the organization would be available to those suffering from handicapping conditions. He pointed out that because of residence requirements, the refugees would not be eligible for services of tax-supported agencies. The Easter Seal societies, he said, hope to be able to offer rehabilitative services to those needing them in the interim period while the refugees are establishing new residences.

Address: The National Society for Crippled Children and Adults, 11 South LaSalle Street, Chicago 3, Illinois. FRanklin 2-0390. Catharine Bauer, Director of Information.

PSYCHIATRIC RESEARCH PROJECT AT SING SING

Dr. Samuel Dunaif has been appointed to carry out a joint psychiatric research project at Sing Sing Prison for the State Departments of Mental Hygiene and Correction, as announced by Commissioner of Mental Hygiene Paul H. Hoch, M.D. and Correction Commissioner Thomas J. McHugh. He will assume his new position as principal research scientist on January 17, 1957.

Serving on a part-time basis, Dr. Dunaif will set up a pilot study to delineate, wherever possible, the areas of research concerning the psychiatry of various types of offenses.

Some of the areas Dr. Dunaif will explore include the problem of recidivism (relapse into prior criminal habits) and how recidivists differ from non-recidivists, whether recidivism can be predicted on the basis of an elaborate personality inventory of the kind used for the more narrowly defined study of sex offenders, whether the newer drug therapies will be of any value in control of recidivism and whether the symptom-producing drugs have a different reaction in various types of offenders, particularly in those who commit offenses against the person as compared with those committing offenses against property. He also will follow cases already treated with shock therapy and attempt to measure the relationship between length of sentence and subsequent recurrence of the offense.

Dr. Dunaif is in private practice and is an instructor in psychiatry at Columbia University College of Physicians and Surgeons. He served as a resident research psychiatrist for two years and as a consultant research psychiatrist for one year on a previous study on convicted sex offenders at Sing Sing.

CERTIFIED DECEMBER 10 AND 11, 1956

The American Board of Psychiatry and Neurology, Inc., New York, N. Y.

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